

# Adenocarcinoma of the Cervix

## *Expression and Clinical Significance of Estrogen and Progesterone Receptors*

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**BACKGROUND.** Although hormone receptor status is an important prognostic indicator in adenocarcinoma of the breast and the endometrium, few studies have investigated the expression and clinical significance of estrogen receptor (ER) and progesterone receptor (PgR) in adenocarcinoma of the cervix.

**METHODS.** ER and PgR expression were determined using an immunohistochemical method in 84 cervical adenocarcinomas. Clinical features and outcome were determined by chart review.

**RESULTS.** ER was identified in 17 of the 84 cases (20%). ER positivity was most frequently detected in mucinous adenocarcinoma of the endocervical type (in 11 of 48 cases) and endometrioid adenocarcinoma (in 4 of 10 cases). PgR was identified in 23 of the 84 cases (27%). PgR positivity was also most frequently detected in mucinous adenocarcinoma of the endocervical type (in 15 of 48 cases) and endometrioid adenocarcinoma (in 6 of 10 cases). Mucinous adenocarcinoma of the intestinal type (five cases), glassy cell carcinoma (two cases), and clear cell adenocarcinoma (two cases) were uniformly negative for both ER and PgR. No association was detected between International Federation of Gynecology and Obstetrics stage and receptor status, but there was a somewhat lower frequency of ER positivity in poorly differentiated tumors ( $P = 0.07$ ). No association was detected between PgR status and disease free survival. Similarly, no association between ER status and overall survival was observed. Although ER positive tumors may be associated with longer disease free survival than ER negative tumors, this difference did not reach statistical significance in this study ( $P = 0.06$ ).

**CONCLUSIONS.** ER and PgR positivity were found in 20% and 27%, respectively, of primary cervical adenocarcinomas. However, receptor status was not significantly associated with either overall survival or disease free survival. *Cancer* 1997; 79:505-12. © 1997 American Cancer Society.

**KEYWORDS:** cervical adenocarcinoma, estrogen receptors, progesterone receptors, survival.

**E**strogen receptor (ER) and progesterone receptor (PgR) status is a well recognized prognostic indicator in women with breast carcinoma and may be of clinical importance in women with endometrial carcinoma.<sup>1,2</sup> In women with breast carcinoma, hormone receptor status is routinely used as a guide for designing therapy. There are also data to suggest that ER and PgR status may be of importance in women with invasive adenocarcinoma of the cervix. Biochemical and immunohistochemical studies have identified ER and PgR in the endocervical columnar epithelium and the normal endocervix appears to be the target tissue of steroid hormones because the quantity and quality of endocervical mucus fluctuates in response to hormonal changes during the menstrual cycle.<sup>3</sup>

Relatively few studies have investigated associations between ER

and PgR status and known prognostic indicators or clinical outcome in women with invasive cervical adenocarcinoma and the results of these studies are somewhat conflicting.<sup>4,5</sup> In this study, we have attempted to clarify the associations between ER and PgR status, known prognostic indicators, and clinical outcome in women with invasive adenocarcinoma of the cervix. The receptor status of 84 cases of predominantly early stage, invasive, primary cervical adenocarcinoma was assessed using an immunocytochemical method and associations between hormone receptor status and tumor histologic subtype, tumor grade, clinical stage, and clinical outcome were investigated.

## **MATERIALS AND METHODS**

### **Case Selection**

Primary cervical adenocarcinomas diagnosed between 1982 and 1993 were obtained from the pathology files of the College of Physicians and Surgeons of Columbia University, New York, New York, M. D. Anderson Cancer Center, Houston, Texas, Royal Victoria Hospital, Montreal, Quebec, and St. Mary's Hospital, Manchester, United Kingdom. Cases were selected specifically to include predominately International Federation of Gynecology and Obstetrics (FIGO) Stage I and Stage II lesions.<sup>6</sup> A variable number of hematoxylin and eosin stained histologic slides were available for review from each case. In some cases, patients had undergone hysterectomy and the entire cervix was available for histologic examination; in other cases, patients had been treated with radiation and only a cervical biopsy obtained prior to therapy was available for assessing histologic type and histologic grade. All cases in which there was clinical or pathologic uncertainty as to the primary site of the tumor were excluded from the study. One hundred and thirty-eight cases were initially identified at these institutions and, of these, 84 cases were eligible for this analysis.

Twenty-four cases were not classified as adenocarcinomas: clear cell adenosquamous carcinoma of the cervix, 11 cases; adenocarcinoma in situ, 10 cases; small cell carcinoma, 1 case; and adenosquamous carcinoma, 2 cases. Twenty-three cases lacked sufficient tissue for ER/PR analysis. Seven cases lacked clinical or follow-up information.

Medical records were reviewed for demographic and clinicopathologic information including date of birth, race/ethnic group, date of diagnosis, histologic diagnosis, clinical FIGO stage, cell type, grade of differentiation, treatment, date of last follow-up, status at last follow-up, and recurrence using a standardized data abstract form. This study was approved by the Institutional Review Board of Columbia University.

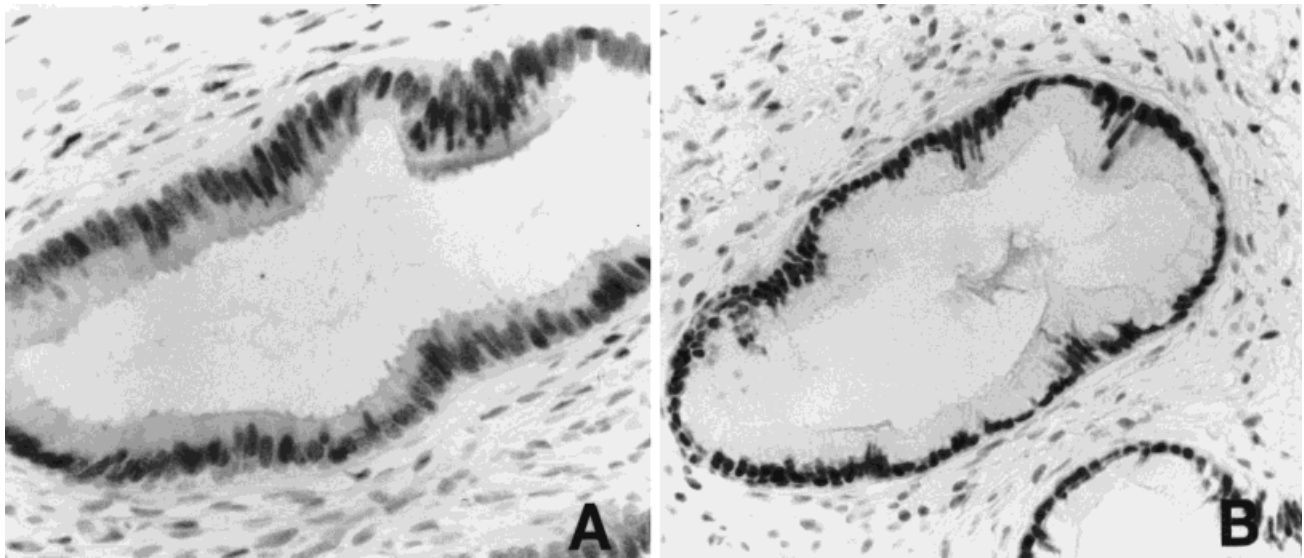
### **Histopathology and Immunocytochemical Analysis for ER and PgR**

The tumors were classified by specific histologic subtypes using previously published criteria.<sup>7,8</sup> In some cases special stains (mucicarmine and periodic acid-Schiff stain with and without diastase) or immunocytochemistry (carcinoembryonic antigen [CEA], vimentin, and cytokeratin) were used in addition to routine hematoxylin and eosin staining to clarify the origin of the tumor. All cases were graded into well differentiated (Grade 1), moderately differentiated (Grade 2), and poorly differentiated (Grade 3) according to the extent of glandular differentiation and extent of cytologic atypia.<sup>7</sup>

For immunohistochemistry, 4- $\mu$ m sections were mounted on silane-coated slides (Digene Diagnostics, Silver Spring, MD) and stained by the streptavidin-biotin method using primary monoclonal antibodies against ER (ERID5, mouse, 1:40; AMAC, Westbrook, MA) and PgR (PRI, mouse 1:1; CAS, Elmhurst, IL).<sup>9</sup> Prior to staining, sections were treated with 0.3% hydrogen peroxide diluted in methanol to block endogenous peroxidase activity and incubated with normal goat serum. Sections used for identifying ER and PgR were treated with microwave irradiation in phosphate-buffered saline (PBS) prior to staining. The sections were then incubated for 18 hours at 4 °C with the primary antibodies followed by treatment with biotinylated goat antimouse secondary antibody (PATHWAY—HRP Detection System; Becton Dickinson, San Jose, CA) diluted 1:10 in the manufacturer's buffer. After 1 hour, the slides were rinsed three times in PBS and streptavidin-biotin peroxidase complex (PATHWAY—HRP Detection System) diluted 1:10 in the manufacturer's buffer was added. The slides were incubated for 1 hour, rinsed twice in PBS, and then reacted with diaminobenzidine chromagen (Dako Corporation, Carpinteria, CA) at 0.375 mg/ $\mu$ L with 0.003% hydrogen peroxide to develop the peroxidase reaction. With each staining reaction a positive control comprised of tissue known to contain the relevant antigen, as well as a negative control of normal mouse immunoglobulin G rather than the primary antibody, was included. All immunohistochemical evaluation was done without knowledge of the clinical and pathologic features of the tumors. Samples containing any individual cells with nuclear staining were classified as positive.

### **Statistical Analysis**

Variables of interest were categorized in the following way: age (<50 years vs.  $\geq$ 50 years); histologic type (mucinous adenocarcinoma of the endocervical type, endometrioid, poorly differentiated adenocarcinoma, or other), grade of differentiation (well, moderately, or



**FIGURE 1.** Immunohistochemical staining for (A) estrogen receptor (ER) or (B) progesterone receptor (PgR) in normal endocervical glands. The nuclei of endocervical glandular cells and fibroblastic-like stromal cells of the cervix stained strongly positive for both ER and PgR (A and B, objective magnification  $\times 40$ ).

poorly differentiated), clinical stage (Stage I vs. Stage  $\geq$  II), and ER and PgR status (positive vs. negative). Descriptive statistics, cross-tabulations, and survival analysis were conducted using SPSS software.<sup>10</sup> Statistical differences between ER and PgR status and clinicopathologic characteristics were assessed using the chi-square test or Fisher's exact test. The Kaplan–Meier method was used to estimate the effect of hormone receptor status on overall survival and disease free survival. Overall survival was defined as the length of time from date of diagnosis to death and disease free survival as the length of time from date of diagnosis to the date of first recurrence. Differences in overall survival or disease free survival curves were estimated by the log rank test. A probability level  $\leq 0.05$  was considered to represent statistical significance.

## RESULTS

### Clinical Features

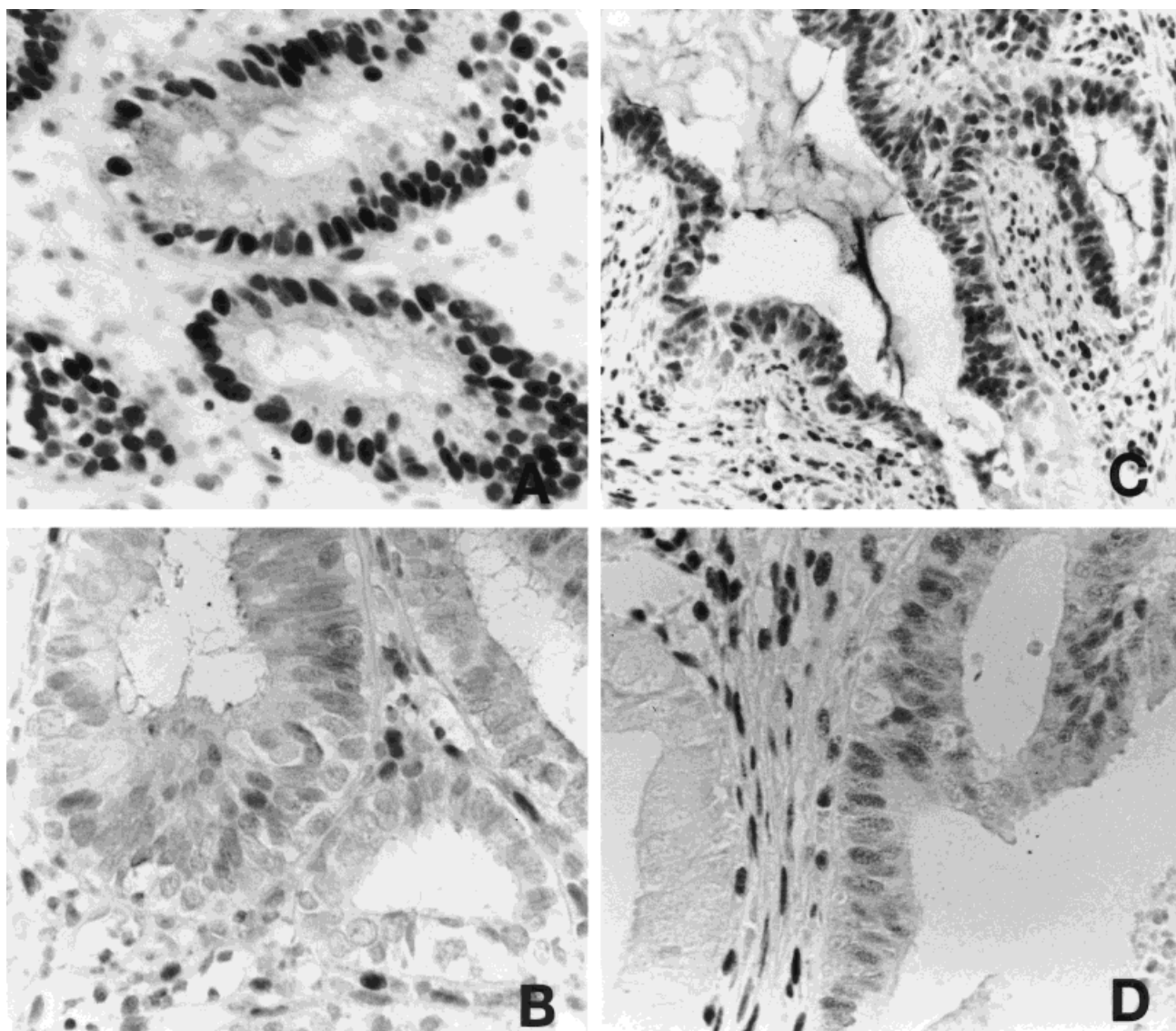
The median age of patients at diagnosis was 42 years (range, 23–84 years). Sixty-two of the 84 women (74%) were younger than 50 years and 22 (26%) were 50 years or older. Sixty of the patients (71%) were white; 14 (17%) were Hispanic; 6 (7%) were black; 1 (1%) was Asian; and 3 (4%) were of unknown racial/ethnic group. The most common histologic type was endocervical (57%). Sixty-eight of the patients (81%) had FIGO Stage I tumors, 11 (13%) had Stage II or higher tumors, and 5 (6%) were unstaged. Approximately 70% (59 tumors) were classified as well or moderately dif-

ferentiated. The median follow-up time from diagnosis for the entire cohort was 43 months (range, 2–107 months). During the study period, 29 patients (35%) had a recurrence and 31 (37%) died. The median survival time among patients who died was 25 months (range, 4–107 months), whereas the median follow-up among patients alive at the end of the study was 52 months (range, 2–93 months).

### ER and PgR Immunocytochemistry

In all cases, normal endocervical cells and fibroblastic-like stromal cells of the cervix stained positively for ER and PgR (Fig. 1). The staining for ER and PgR was restricted to the nucleus of the cells and cytoplasmic staining was not observed. Seventeen of the 84 primary cervical tumors (20%) stained positively for ER and 23 (27%) stained positively for PgR. The staining pattern in the tumor cells was similar to that observed in the normal endocervical cells and was restricted to the nucleus (Fig. 2). However, the intensity and distribution of ER and PgR staining in the tumor tissue was more heterogeneous than that observed in the normal tissues. ER and PgR staining in individual tumor cases would often vary from strongly positive to completely negative (Fig. 2). In the tumors, staining for both ER and PgR was frequently observed in the nuclei of nonneoplastic stromal cells surrounding the tumor cells.

The two histologic subtypes most commonly associated with ER and PgR positivity were mucinous adenocarcinomas of the endocervical type and endometrioid subtypes (Table 1). None of the 5 adenocarcinomas of an



**FIGURE 2.** Immunohistochemical staining for (A and B) estrogen receptor (ER) or (C and D) progesterone receptor (PgR) in invasive cervical adenocarcinoma. ER and PgR staining varied from (A and C) strong and homogeneously positive to (B and D) weakly and heterogeneously positive in carcinoma cases (A, B, and D, objective magnification  $\times 40$ ; C, objective magnification  $\times 20$ ).

intestinal subtype, neither of the 2 glassy cell carcinomas, neither of the 2 clear cell carcinomas, and only 1 of the 11 poorly differentiated adenocarcinomas stained positively for either ER or PgR.

The relationship between histologic grade and ER and PgR positivity is shown in Figure 3. ER positivity was somewhat reduced in poorly differentiated (Grade 3) tumors compared with well differentiated and moderately differentiated (Grade 1 and 2) tumors ( $P = 0.07$ ). In contrast, no reduction in PgR positivity was observed with increasing tumor grade. Predominately early stage tumors were initially selected for this series (Stage I and Stage II). Sixty-eight of the 84 cases (81%) were Stage I

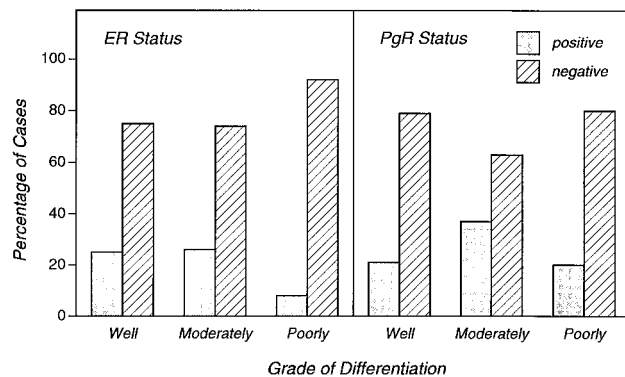
and only 11 (13%) were Stage II or higher. Although our ability to evaluate associations between ER and PgR status and tumor stage was limited by our initial selection of early stage tumors, no significant difference was observed between tumors that were Stage I and those that were Stage II or higher with respect to ER and PgR positivity (Figure 4). Similarly, no statistically significant differences in ER and PgR status were observed with age and racial/ethnic group.

#### **ER and PgR Status as a Clinical Prognosticator**

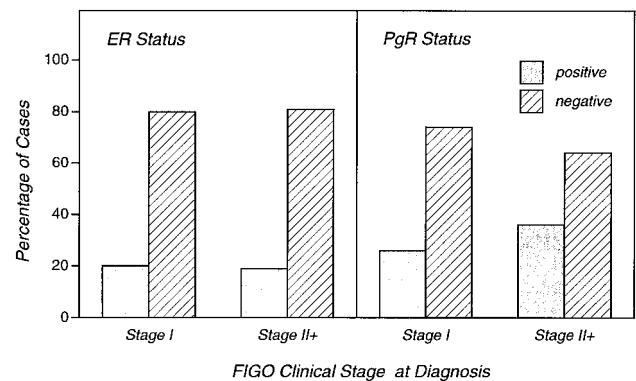
No statistically significant differences in overall survival or disease free survival were observed between

**TABLE 1**  
Steroid Hormone Receptor Status of Specific Histologic Subtypes of Cervical Adenocarcinoma

Histologic subtype	No. of cases	Estrogen receptor status No. of cases (% of total)		Progesterone receptors No. of cases (% of total)	
		Positive	Negative	Positive	Negative
Mucinous adenocarcinoma					
Endocervical type	48	11 (23%)	37 (77%)	15 (31%)	33 (69%)
Intestinal type	5	0	5 (100%)	0	5 (100%)
Endometrioid adenocarcinoma	10	4 (40%)	6 (60%)	6 (60%)	4 (40%)
Clear cell adenocarcinoma	2	0	2 (100%)	0	2 (100%)
Glassy cell carcinoma	2	0	2 (100%)	0	2 (100%)
Poorly differentiated adenocarcinoma	11	1 (9%)	10 (91%)	1 (9%)	10 (91%)
Adenoid basal carcinoma	2	1 (50%)	1 (50%)	1 (50%)	1 (50%)
Adenoid cystic carcinoma	1	0	1 (100%)	0	1 (100%)
Minimal deviation adenocarcinoma	1	0	1 (100%)	0	1 (100%)
Serous adenocarcinoma	1	0	1 (100%)	0	1 (100%)
Villoglandular adenocarcinoma	1	0	1 (100%)	0	1 (100%)



**FIGURE 3.** Influence of histologic grade on estrogen receptor (ER) and progesterone receptor (PgR) positivity in invasive primary adenocarcinoma of the cervix.



**FIGURE 4.** Influence of International Federation of Gynecology and Obstetrics clinical stage on estrogen receptor (ER) and progesterone receptor (PgR) positivity in invasive primary adenocarcinoma of the cervix.

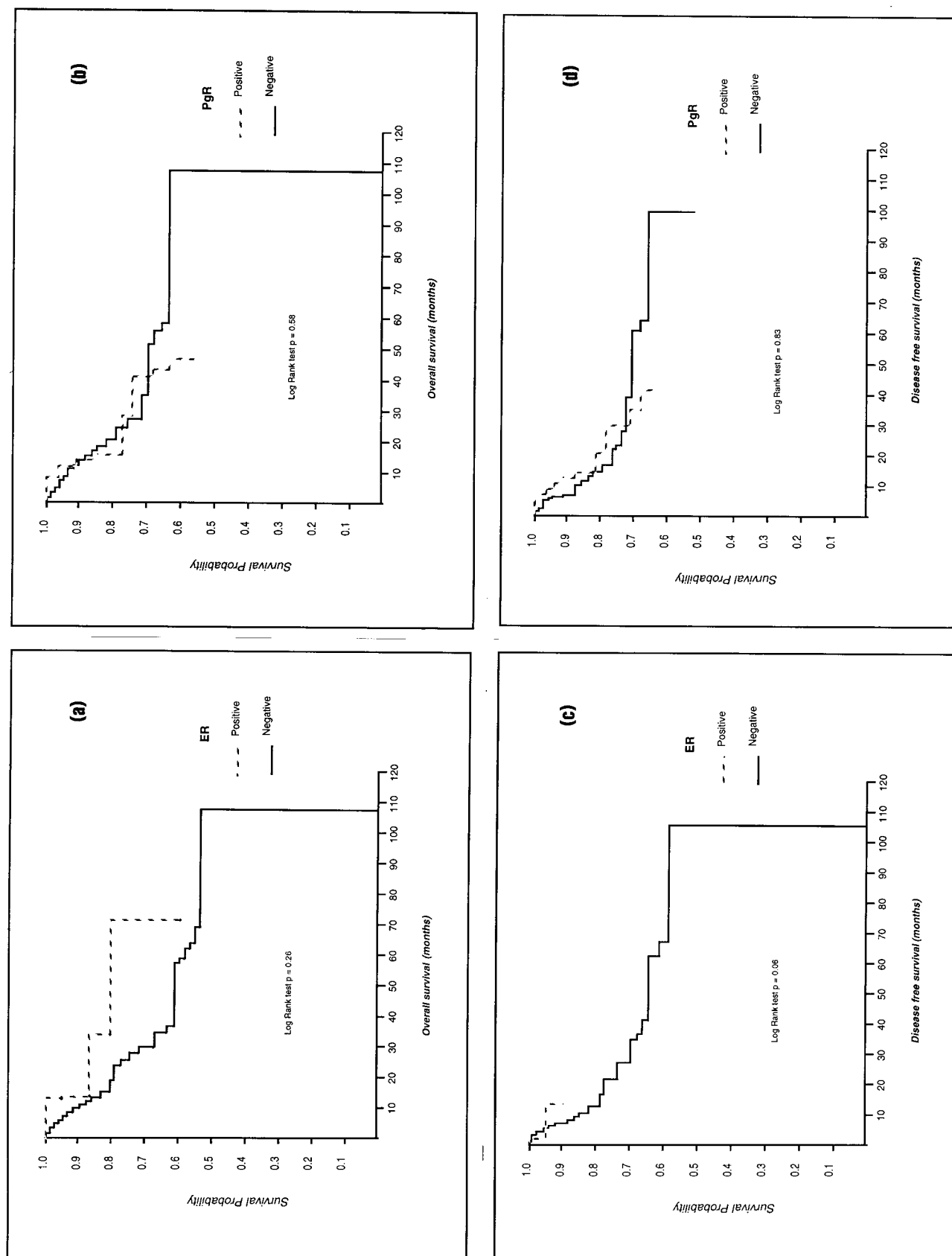
PgR positive and PgR negative cases (Fig. 5). Similarly, no statistically significant difference was observed between patients with ER positive and ER negative tumors. Although the current data suggested that women with ER positive tumors may have longer disease free survival than women with ER negative tumors ( $P = 0.06$ ), this finding must be interpreted with caution because it did not reach statistical significance ( $P = 0.06$ ).

## DISCUSSION

Over the last several decades the relative proportion of invasive adenocarcinomas to invasive squamous cell carcinomas of the cervix has been increasing and several studies have reported an increase in the absolute number of cervical adenocarcinomas.<sup>11–13</sup> These increases have heightened interest in the pathogenesis and management of women with invasive adenocarci-

noma of the cervix.<sup>14–18</sup> Most studies have reported that risk factors and prognostic indicators for women with adenocarcinomas are similar to those for women with squamous cell carcinomas of the cervix.<sup>16,19</sup> The major prognostic indicators for both histologic types include FIGO clinical stage, histologic grade, size of the lesion, lymph-vascular space involvement, and lymph node metastases.<sup>20–25</sup> One possible prognostic indicator that might be expected to be more important for cervical adenocarcinomas than for squamous cell carcinomas is steroid hormone receptor status.

Several studies have measured ER and PgR in cervical carcinomas. Using biochemical assays, ER has been detected in 34–56% of cervical carcinomas and PgR in 15–58%.<sup>26–29</sup> However, the prognostic significance of hormone receptor status remains unclear. Some studies have found that ER or PgR status has no significant impact on either disease free survival or



**FIGURE 5.** Influence of ER and PgR positivity on disease free survival and overall survival of women with invasive primary adenocarcinoma of the cervix.

length of overall survival in women with primary invasive cervical carcinoma, whereas other studies have found hormone receptor status to be a significant prognostic indicator.<sup>26-29</sup> Potish et al. reported that both ER and PgR positivity were independently associated with enhanced overall survival in premenopausal, but not postmenopausal, women with invasive cervical carcinoma, whereas Hunter et al. found a weak association between survival and PgR positivity, but not with ER positivity.<sup>26,27</sup> However, these studies were of women with all histologic types of cervical carcinoma, and relatively few cases of primary invasive adenocarcinoma of the cervix were included.

Only two previously published studies have specifically analyzed the clinical significance of ER and PgR status in primary invasive adenocarcinomas of the cervix. Masood et al. assessed ER and PgR status in a series of 54 women with primary cervical adenocarcinoma and found that patients with either ER or PgR positive tumors had significantly improved overall survival compared with patients with ER and PgR negative tumors.<sup>4</sup> However, another study of ER and PgR status in 47 women with primary cervical adenocarcinoma found an increase in disease free survival among women with ER positive tumors but not with PgR positive tumors.<sup>5</sup> The current series assessed hormone receptor status in 84 women with primary invasive cervical adenocarcinoma. No statistically significant difference in overall survival or disease free survival between women with PgR positive and PgR negative tumors was observed. Similarly, no difference was detected between women with ER positive and ER negative tumors. The current data suggested an increased disease free survival of borderline statistical significance ( $P = 0.06$ ) among women with ER positive tumors; however, the interpretation of this result is limited by the number of events observed in this group.

The reason for the different results obtained by these three studies with respect to associations between hormone receptor status and clinical outcome is unclear. All three series have included women with predominately FIGO Stage I and Stage II carcinomas, and all three used an immunohistochemical method to assess ER and PgR status. However, in the current series only 20% of the cases were classified as ER positive, whereas 30% of the cases in the series of Masood et al. and 26% of the cases in the series of Ghandour et al. were classified as ER positive.<sup>4,5</sup> These three series have also obtained different results with respect to associations between hormone receptor status and tumor grade. In both the current series and the series of Masood et al.,<sup>4</sup> ER positivity was inversely associated with histologic grade, whereas no association between histologic grade and ER positivity was observed

by Ghandour et al.<sup>5</sup> However, it should be noted that all three studies have found similar results with respect to associations between specific histologic subtypes of invasive cervical adenocarcinoma and hormone receptor positivity. Mucinous adenocarcinomas of the endocervical type and endometrioid carcinomas have the highest rate of ER and PgR positivity. Mucinous adenocarcinomas of the intestinal type, clear cell carcinomas, and glassy cell carcinomas have been found to be uniformly ER and PgR negative.<sup>4,5</sup>

In conclusion, the current data failed to confirm that either ER or PgR status is a useful prognostic factor in women with cervical adenocarcinoma. Further assessment of the impact of ER and PgR status on the clinical outcome of patients with primary invasive adenocarcinoma of the cervix in larger case series is needed. In addition, this study was limited to assessing the impact of ER and PgR status on outcome and additional studies assessing the impact of other potential biomarkers and risk factors including human papillomavirus DNA and Ki-67 status in women with invasive cervical adenocarcinomas are needed. Larger studies will also allow a more detailed analysis of the role of hormone receptor status in less frequent histologic subtypes that showed interesting patterns of steroid hormone receptor status.

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