

Cytoplasmic Estradiol and Progesterone Receptors in the Normal and Cancerous Tissues of the Uterine Cervix

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Abstract—The changing patterns of estradiol receptor(E₂R) and progesterone receptor(PR) contents of the normal and cancerous tissues of the cervix were analyzed and the results were summarized as follows:

1. In the premenopausal group, E₂R contents were significantly elevated in the secretory phase than in the proliferative phase but PR contents showed no difference. In the postmenopausal cervix, PR contents showed an apparent decrease than in the premenopause. And the positive rates of both receptors dropped significantly in postmenopausal group compared to premenopause ($p < 0.05$).

2. The effect of gravidity and parity of E₂R and PR contents was not evident except significant decrease in E₂R contents in the group of parity of more than 5.

3. Correlation between E₂R and PR contents in the normal cervical tissues was significant in the premenopause but not in the postmenopause.

4. Cancerous changes from the normal cervical tissues had no effect on E₂R and PR

5. PR contents in the non-keratinizing cervical carcinoma were significantly higher than in the keratinizing type ($p < 0.05$) but change of E₂R contents was not prominent.

6. The relationship of E₂R and PR contents of cervical carcinoma with clinical stage and histopathologic parameters such as nuclear grade, mitotic rate, and lymphoid infiltration was not significant.

Key word: *Cytoplasmic receptor, Estradiol, Progesterone, Normal tissue, Cancer, Uterine cervix*

INTRODUCTION

It is at present generally accepted that all the main group of steroids—estrogens, progesterones, androgens, and glucocorticoids—have a similar basic mechanism of action in their respective target tissue; that is, after permeation through the cell membrane, the steroid binds specifically and with high affinity to a soluble cytoplasmic receptor, and the resulting steroid-receptor complex undergoes a structural change (activation) prior to its translocation to the nucleus, where binding to a chromatin acceptor site takes place. Nuclear binding of the steroid-receptor complex facilitates the gene transcription, leading to the enhanced production of the

various RNA species and eventually to the augmented protein synthesis (Baulieu *et al.* 1975; Janne *et al.* 1975; Chan and O'Malley 1976).

Characterization of steroid receptors has been carried out in connection with various clinically relevant problems, and for several years the measurement of steroid receptor contents has been proven to be clinically useful in the selection of treatment modalities for the breast carcinoma patients (Hawkins *et al.* 1980; Knight *et al.* 1980; Vihko and Isolato 1981). The data currently available strongly suggest that the routine measurement of steroid receptor in the endocrine-dependent gynecologic normal and cancerous tissues will be clinically beneficial. Several studies (Spona *et al.*

1979; Levy *et al.* 1980) have shown that the normal uterine endometrium contains detectable concentration of estradiol (E_2R) and progesterone receptors (PR), which vary during the cycle due to the effect of the steroid hormones.

Among the gynecologic malignancies, E_2R and PR contents of endometrial cancer tissues have been most extensively studied. Relations of E_2R and PR contents with the tumor grade (Creasman *et al.* 1980; Ehrlich *et al.* 1981), the histopathologic parameters (Zaino *et al.* 1983), the response to the endocrine therapy (Creasman *et al.* 1980; Kauppila *et al.* 1980) and possibly the prognosis (Creasman *et al.* 1980) of the endometrial carcinoma have been recently studied.

But in the cases of cervical carcinoma, the study on E_2R and PR contents and its relationship to the tumor grade and histopathologic findings showed conflicting results (Martin and Hahnel 1978; Bloch 1979; Soutter *et al.* 1981; Ford *et al.* 1983; Gao *et al.* 1983).

Furthermore, in Korea, there has been no effort so far in this field of E_2R and PR analysis in the normal and cancerous uterine tissues except some of the reports on the E_2R and PR levels in the breast cancers (Kim *et al.* 1981; Kim *et al.* 1982; Kim *et al.* 1982).

Therefore the present study has been carried out with the following purposes: first, to elucidate the varying mode of E_2R and PR contents in the normal cervical tissues in response to normal menstrual cycle and the effects of the menopause, gravidity and parity; second, to identify the correlation between E_2R and PR contents in the normal cervical tissues; third, to compare the difference of E_2R and PR contents in the normal and cancerous tissues of the cervix; and fourth, to pursue the relationship of E_2R and PR contents with histopathologic parameters of the cervical cancer tissues.

MATERIALS AND METHODS

Samples

Normal premenopausal cervical tissues consisted of 14 cases of proliferative phase and 12 cases of secretory phase of endometrial cycle. Included also were 4 postmenopausal normal cervical tissues, 5 cervical intraepithelial neoplasia, and 10 cervical carcinomas in this study.

Collection and storage of the samples

The cervical samples for receptor analysis and pathological studies were collected at Department of Obstetrics and Gynecology in National Medical

Center and Seoul National University Hospital by cone biopsy or surgical resection. Right after collection, they were washed with normal saline and then divided into two parts; one part for pathological examination and the other part was rapidly frozen and stored immediately in the liquid nitrogen tank (Apollo SX-34, MVE Cryogenics) until receptor assay.

Reagents

Chemicals were purchased from the following sources: estradiol, diethylstilbesterol, PPO (2,5-diphenyloxazole), POPOP [1,4-bis (5-phenyl-2-oxazolyl)-benzene], dithiothreitol (Sigma Chemical Co., St. Louis, U.S.A.); (2,3,6,7- H^3) estradiol (110 Ci/mM), (17 alpha methyl H^3), promegestone (87 Ci/mM), cold promegestone (R 5020) (New England Nuclear Co., Boston, U.S.A.); Dextran T-70 (Pharmacia Fine Chemicals AB Co., Uppsala, Sweden), activated charcoal (Merck Co., Rahway, U.S.A.) and other chemicals were purchased as analytical grade from commercial companies.

Preparation of the samples

The samples were minced and homogenized in approximately five volumes of TED buffer (Tris 10 mM, EDTA 1.5 mM, dithiothreitol 0.5 mM, glycerol 10% (v/v), pH 7.4) with Polytron homogenizer (Biotron, Swiss). It worked 15 seconds and rested 45 seconds on the ice bath 4 times. The homogenate was centrifuged at 105,000 x g for one hour with Beckman L 80 ultracentrifuge and the resulting supernatant was collected for the subsequent receptor analysis and protein determination (Fig. 1).

Protein measurement

Protein content in the sample was determined after modified Lowry's method (Lowry *et al.* 1951; Oyama and Eagle, 1956).

Estradiol receptor analysis

For the analysis of cytoplasmic E_2R contents in the cervical tissues, the dextran-coated charcoal method (DCC) of McGuire (1973) was modified as follows; in the first set of the tubes, each 10 ul of hot estradiol (25 fmol, 50 fmol, 100 fmol, 200 fmol) in ethanol was added. And in the second set of the tubes, each 10 ul of cold diethylstilbesterol (5 pmol, 10 pmol, 20 pmol, 40 pmol) was added respectively. Into all of these tubes, each 200 ul of the cytosol from the sample was added and vortexed briefly and each tube was mixed for one hour at 4 C. After incubation, each 500 ul of DCC solution (0.25% activated charcoal, 0.025% Dextran T-70, Tris buffer, pH 8.0) was added with vortex-

ing and the tubes were further mixed for 10 minutes at 4°C and were centrifuged at 3,000 x g for 20 minutes (IES, Refrigerated Centrifuge). Then each 500 ul of the supernatant was mixed into 10

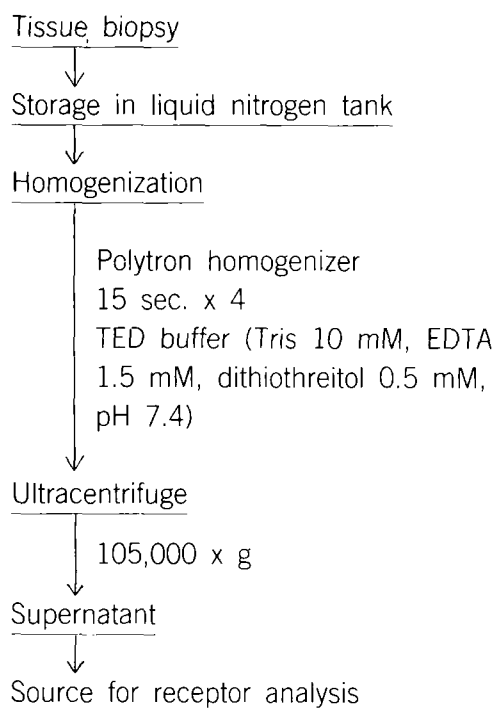


Fig. 1. Preparation of the samples.

ml of the scintillation cocktail (Toluene 667 ml, Triton X-100 333 ml, PPO 5.5 gm, POPOP 0.1 gm), and the radioactivity of the sample was monitored by Packard Tricarb B 2450 liquid scintillation spectrophotometer (Fig. 2).

Progesterone receptor analysis

For the analysis of PR contents in the cervical tissues, the basic mode of the procedure was same as that for the E₂R analysis except for the use of radioactive synthetic progesterone, promegestone for hot estradiol, and cold promegestone for diethylstilbesterol as nonspecific binding competitor (Fig. 2).

Single saturation dose analysis

For the analysis of E₂R and PR contents in these samples, the single saturation dose analysis method (McGuire *et al.* 1973) was adopted with the following modification. To achieve the higher binding capacity of the receptor in the samples, the hot estradiol content was increased to 400 fmol, rather than 200 fmol for E₂R analysis, and hot promegestone was 1,200 fmol rather than 200 fmol for PR analysis. To exclude the nonspecific binding in each case, the 200 fold excess of diethylstilbes-

Tube number	1-1	1-2	2-1	2-2	3-1	3-2	4-1	4-2
Hot E ₂ (or hot promegestone) (fmol per tube)	25		50		100		200	
Cold DES (or cold promegestone) (pmol per tube)		5		10		20		40
Cytosol (ul)	200	200	200	200	200	200	200	200
	Vortex briefly and mix at 4°C for one hour							
Hot E ₂ (or hot promegestone) (fmol per tube)		25		50		100		200
	Vortex briefly and incubate at 4°C overnight							
DCC solution (ul)	500	500	500	500	500	500	500	500
	Centrifuge 3,000 x g for 20 minutes at 4°C							
	↓							
	500 ul of supernatant from each tube							
	↓							
	Radioactivity monitoring							

Fig. 2. Receptor analysis.

terol for E₂R and cold promegestone for PR was added respectively.

Histopathologic analysis

The specimen were examined routinely by the histopathologic criteria and cervical carcinoma was graded semiquantitatively with respect to cell type, nuclear grade, mitotic rate, and density of lymphoid infiltration according to Zaino *et al.* (1983).

Data analysis

For the analysis of E₂R and PR contents, the Scatchard plot analysis was carried out for multi-point assays (Fig. 3), and single specific binding capacity was calculated for the single saturation dose analysis and all the data were converted on the base of unit protein content (mg). For the com-

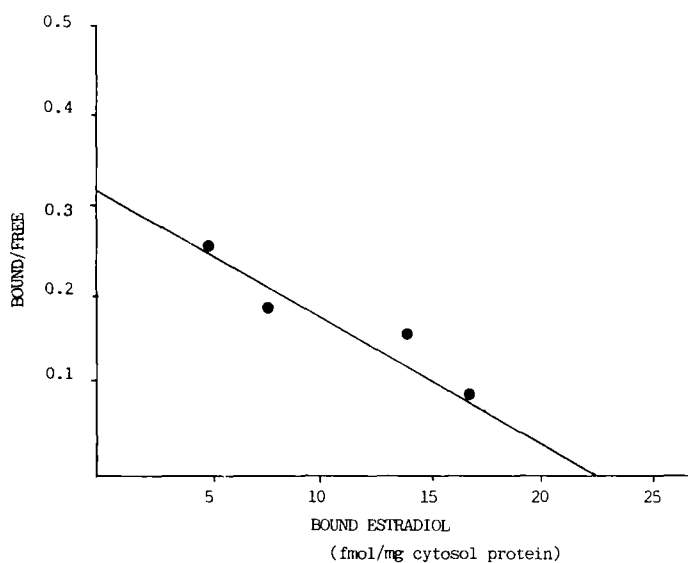


Fig. 3. Example of Scatchard plot analysis for estradiol receptor analysis.

parison between the groups, the statistical analysis of the data was conducted by Student's t test and rank sum test.

RESULTS

E₂R and PR contents of the normal cervical tissues in the normal menstrual cycle

E₂R and PR contents in the normal cervical tissues were analyzed in respect to periodical change, such as proliferative and secretory phase and menopausal status.

As shown in Table 1, E₂R and PR contents of the normal cervical tissues were shown to be higher in the secretory than in the proliferative phase. In other words, the mean value of E₂R in the proliferative phase was 7.5 fmol/mg protein, while that in the secretory phase was 21.8 fmol/mg protein (p < 0.05). And the mean value of PR content was 23.6 fmol/mg protein in the proliferative phase and 32.3 fmol/mg protein in the secretory phase. When E₂R and PR contents in the cervical tissues were compared by the pre- and postmenopausal status, the mean value of E₂R contents was lower in premenopause (14.1 fmol/mg protein) than in the postmenopause (25.5 fmol/mg protein) and that of PR contents was lower in the postmenopause (19.0 fmol/mg protein) than in the premenopause (27.6 fmol/mg protein).

The positive rates of E₂R and PR in the normal cervical tissues were compared. The positivity was defined as the value higher than 3 fmol/mg protein for E₂R and 10 fmol/mg protein for PR. The changing pattern of positive rate of both receptors in the normal cervical tissue was contrasting. As summa-

Table 1. Comparison of estradiol and progesterone receptor contents in the normal cervix according to the menstrual status[†]

Menstrual status	Number of cases	Estradiol receptor (fmol/mg cytosol protein) Mean ± S.E.M.	Progesterone receptor (fmol/mg cytosol protein) Mean ± S.E.M.
Premenopause			
Proliferative phase	14	7.5 ± 2.2	23.6 ± 12.6
Secretory phase	12	21.8 ± 5.6*	32.3 ± 7.0
Total	26	14.1 ± 3.2	27.6 ± 8.3
Postmenopause	4	25.5 ± 9.1	19.0 ± 12.5

[†]Receptor analysis was done by dextran-coated charcoal method.

S.E.M.: Standard error of mean

* p < 0.05

Table 2. Correlation of the receptor status in the normal cervix with the menstrual status[†]

Menstrual status	E ₂ R+, PR+	E ₂ R+, PR-	E ₂ R-, PR+	E ₂ R-, PR-
Premenopause				
Number of cases	10	8	6	2
%	38	31	23	8
Postmenopause				
Number of cases	0	3	1	0
%	0*	75	25	0

[†]Receptor contents higher than 3 fmol/mg protein and 10 fmol/mg protein are considered E₂R positive (E₂R+) and PR positive (PR+), respectively.

* p < 0.05

Table 3. Effect of gravidity on the estradiol and progesterone receptor contents of the normal cervix

Gravida	Number of cases	Estradiol receptor (fmol/mg cytosol protein) Mean ± S.E.M.	Progesterone receptor (fmol/mg cytosol protein) Mean ± S.E.M.
2-3	8	10.5 ± 3.2	12.8 ± 3.2
4-5	8	18.9 ± 8.2	37.5 ± 15.8
More than 6	10	13.1 ± 4.1	34.8 ± 17.9

S.E.M.: Standard error of mean

Table 4. Effect of parity on the estradiol and progesterone receptor contents of the normal cervix

Parity	Number of cases	Estradiol receptor (fmol/mg cytosol protein) Mean ± S.E.M.	Progesterone receptor (fmol/mg cytosol protein) Mean ± S.E.M.
1-2	6	8.8 ± 4.9	24.0 ± 10.4
3-4	17	16.9 ± 4.2	31.3 ± 11.9
More than 5	3	3.3 ± 1.2*	31.0 ± 18.6

S.E.M.: Standard error of mean

* p < 0.005

rized in Table 2, the positive rate of both of E₂R and PR was 38% in premenopause, while none of the postmenopausal cervix had dual positive E₂R and PR (p<0.05).

Effects of gravidity and parity on E₂R and PR contents in the normal cervical tissues

The relationship of E₂R and PR contents in the normal cervical tissues with gravidity and parity was summarized in Table 3 and 4. As shown in those tables, it was noteworthy that the effect of gravidity on both receptors was not apparent but significant decrease of E₂R contents in the parity of more than 5 was observed. But the small sample size blurred the concrete results.

Relationship of E₂R contents to PR contents in the normal cervical tissues

The correlation between E₂R and PR contents in the normal cervical tissues was analyzed. As shown in Fig. 4, the positive cases of E₂R and PR showed a significant positive correlation in the premenopause ($y = 0.69x + 0.59$, $r = 0.64$, $p < 0.05$) which suggested that the higher E₂R contents, the higher the PR contents would be. But in the postmenopause state, such a relationship was not observed.

Comparison of E₂R and PR contents in the normal and cancerous tissues of the cervix
E₂R and PR contents showed no significant

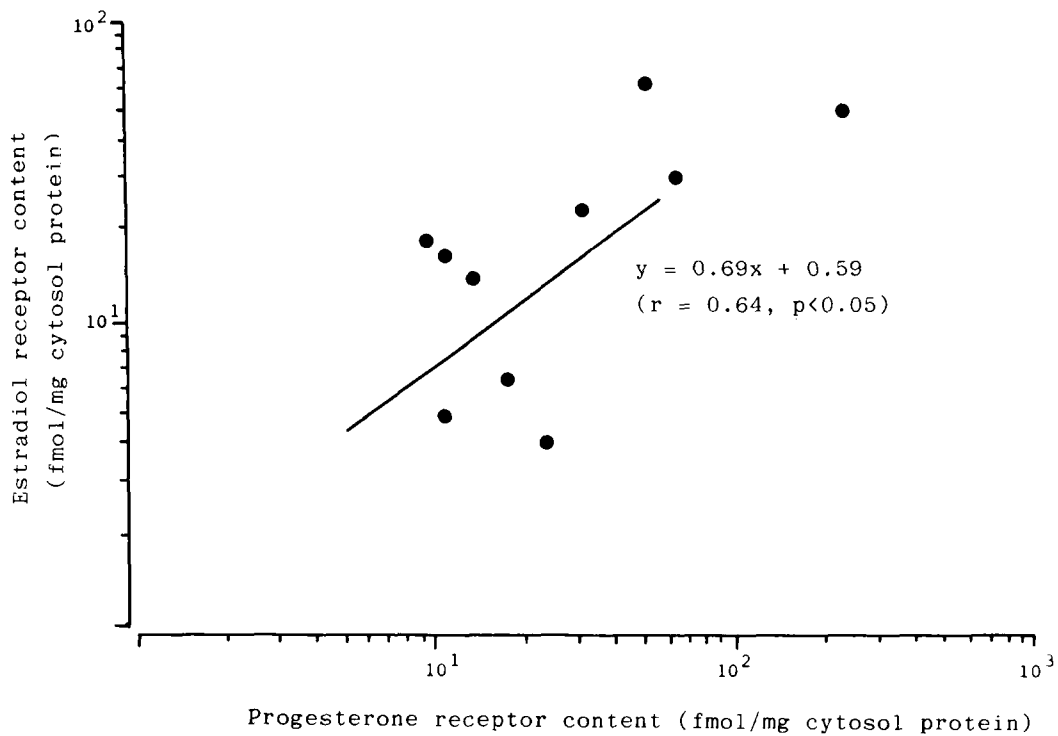


Fig. 4. Correlation between the estradiol and progesterone receptor contents in premenopausal cervical tissues.

Table 5. Comparison of estradiol and progesterone receptor contents between the normal and cancerous tissues of the cervix

Type	Number of cases	Estradiol receptor (fmol/mg cytosol protein) Mean \pm S.E.M.	Progesterone receptor (fmol/mg cytosol protein) Mean \pm S.E.M.
Normal cervix	26	14.1 \pm 3.2	27.6 \pm 8.3
C.I.N.	5	10.4 \pm 9.1	29.2 \pm 12.5
Cx. Ca.	10	14.4 \pm 5.6	20.6 \pm 4.0

S.E.M.: Standard error of mean

C.I.N.: Cervical intraepithelial neoplasia

Cx. Ca.: Cervical carcinoma

changes from the normal cervix to cervical carcinoma (Table 5) and the rate of both E₂R and PR positivity were similar in the normal and cancerous tissues of the cervix (Table 6).

Relationship of clinical stage of cervical carcinoma to E₂R and PR contents

E₂R and PR contents were analyzed according to the clinical stage of cervical carcinoma. As shown in Table 7, there was no significant tendency of change in E₂R and PR contents in relation to clinical stage. However, PR content was observed to be decreased with the advancement of the carcinoma; namely, 32 fmol/mg protein in stage 0 and 17.4 fmol/mg protein in stage II and III.

Relationship of E₂R and PR contents to the presence of keratinization in the epidermoid

cervical carcinoma

In the current study, the presence of keratinization of epidermoid carcinoma showed reducing effect on E₂R and PR contents (Table 8). The mean value of E₂R was 16.3 fmol/mg protein in non-keratinizing tumor and 7 fmol/mg protein in keratinizing type. And the tendency of PR contents was similar to E₂R contents; that is 24.1 fmol/mg protein in non-keratinizing tumor and 6.5 fmol/mg protein in keratinizing type, where the difference was statistically significant ($p < 0.05$). Therefore PR content was reduced in keratinizing epidermoid carcinoma.

Relationship of E₂R and PR contents to the nuclear grade and mitotic rate of cervical carcinoma

Table 6. Correlation of receptor status in the normal and cancerous tissues of the cervix.

Type	E ₂ R+, PR+	E ₂ R+, PR-	E ₂ R-, PR+	E ₂ R-, PR-
Normal cervix				
Number of cases	10	8	6	2
%	38	31	23	8
C.I.N.				
Number of cases	1	1	3	0
%	20	20	60	0
Cx. Ca.				
Number of cases	3	2	5	0
%	30	20	50	0

Table 7. Comparison of the estradiol and progesterone receptor contents with clinical stage of cervical carcinoma

Clinical stage	Number of cases	Estradiol receptor (fmol/mg cytosol protein) Mean ± S.E.M.	Progesterone receptor (fmol/mg cytosol protein) Mean ± S.E.M.
0	3	16.7 ± 14.1	32.0 ± 20.8
I	5	15.8 ± 7.6	23.8 ± 5.3
II, III	5	13.0 ± 9.4	17.4 ± 6.7

S.E.M.: Standard error of mean

Table 8. Correlation of estradiol and progesterone receptor contents with the presence of keratinization in epidermoid cervical carcinoma

Histologic Type	Number of cases	Estradiol receptor (fmol/mg cytosol protein) Mean ± S.E.M.	Progesterone receptor (fmol/mg cytosol protein) Mean ± S.E.M.
Keratinizing	2	7.0 ± 6.1	6.5 ± 5.6
Non-keratinizing	8	16.3 ± 6.7	24.1 ± 4.0*

S.E.M.: Standard error of mean

* p < 0.05

Table 9. Comparison of estradiol and progesterone receptor contents with nuclear grade of cervical carcinoma

Nuclear grade	Number of cases	Estradiol receptor (fmol/mg cytosol protein) Mean ± S.E.M.	Progesterone receptor (fmol/mg cytosol protein) Mean ± S.E.M.
i	2	11.5 ± 10.6	19.1 ± 7.1
II	6	11.8 ± 6.5	22.5 ± 6.8
III	2	25.0 ± 24.2	16.5 ± 0.5

S.E.M.: Standard error of mean

Table 10. Comparison of estradiol and progesterone receptor contents with mitotic rate of cervical carcinoma

Mitotic rate	Number of cases	Estradiol receptor (fmol/mg cytosol protein) Mean ± S.E.M.	Progesterone receptor (fmol/mg cytosol protein) Mean ± S.E.M.
II	5	14.8 ± 9.6	21.8 ± 3.4
III	5	14.0 ± 7.4	19.4 ± 8.1

S.E.M.: Standard error of mean

Table 11. Comparison of estradiol and progesterone contents with density of lymphoid infiltration in cervical carcinoma

Lymphoid infiltration	Number of cases	Estradiol receptor (fmol/mg cytosol protein) Mean ± S.E.M.	Progesterone receptor (fmol/mg cytosol protein) Mean ± S.E.M.
I	4	14.0 ± 9.4	22.5 ± 7.4
II	3	8.0 ± 6.7	26.7 ± 7.8
III	3	21.3 ± 13.8	12.3 ± 4.0

S.E.M.: Standard error of mean

The nuclear grade of cervical carcinoma was defined by the following criteria after Zaino *et al.* (1983): Grade I, oval, regular nuclei with little pleomorphism, inconspicuous or no nucleoli and vesicular chromatin: Grade II, oval to irregular large nuclei with moderate pleomorphism, moderate-sized nucleoli and fine punctate chromatin: Grade III, irregular large nuclei with great pleomorphism, prominent nucleoli and coarsely granular chromatin. The cervical carcinoma in the present study showed no apparent difference in E₂R and PR contents according to the nuclear grade of the cervical carcinoma (Table 9).

The grade of mitotic rate was defined after Zaino *et al.* (1983) as follows: Grade I, fewer than one mitosis per high power field (HPF): Grade II, between one and three mitoses per HPF: Grade III, more than three mitoses per HPF. With increase of mitotic rate, no apparent difference in E₂R and PR contents was observed (Table 10).

Relationship of E₂R and PR contents to the density of lymphoid infiltration in cervical carcinoma

The density of lymphoid infiltration was defined as follows: Grade 0, no mononuclear inflammatory infiltration at the interface of tumor with nonneoplastic tissue: Grade I and II, intermediate densities of lymphoid infiltration surrounding a portion or all of the tumor-nontumor interface: Grade III, heavy

lymphoid infiltration in and around tumor cells (Zaino *et al.* 1983). The result showed that the increase of density of lymphoid infiltration had no significant impact on E₂R and PR contents (Table 11).

DISCUSSION

It has been shown in the steroid receptor study of the gynecologic malignancies that all types of hormonal treatment for carcinoma of the breast, whether additive or ablative, resulted in comparable remission rates, suggesting the strong interdependence between the presence or absence of receptor and the responsiveness of the tumor (Martin and Hahnel 1978). Most of the female genital organs as well as the breast have the high estrogen dependency for growth or differentiation.

Cervical tissue responds to the influence of female sex steroids in a characteristic pattern with production of cervical mucus (Jordan and Singer 1976). The notoriously high incidence of cervical carcinoma among Korean women led this study to concern about the sex steroid effect on the normal and malignant cervical tissues, since the major hormones affecting this female genital organ are estrogen and progesterone. For this purpose, it is pertinent to monitor the receptor contents of these steroids in the cervical tissues, since these receptor contents may indicate the functional status of the

tissue to the hormones (Lippman and Kasid 1984).

There are many conflicting reports on E₂R and PR contents in the cervical tissues; some reported that cytoplasmic E₂R and PR contents fluctuated throughout the menstrual cycle in a manner similar to that found in the corresponding endometrial tissues (Sanborn *et al.* 1975; Sanborn *et al.* 1976), other proved that only PR contents showed higher levels in the proliferative phase while E₂R contents remained constant (Sanborn *et al.* 1978) or highest E₂R contents only at midcycle and rapid decrease thereafter (Holt *et al.* 1979).

In the present study of the normal cervical tissues, E₂R contents were significantly higher in the secretory phase than in the proliferative phase but such a tendency was not observed in the PR contents (Table 1). And the difference in the receptor contents was evident in relation to menopausal status. E₂R contents showed no significant change before and after menopause, but PR contents showed the significant decrease in the postmenopausal status (Table 2), which suggested that the deviation of estradiol and progesterone functional apparatus in the postmenopause has occurred in contrast to synchronizing premenopausal organization. The positive rate of both receptors in premenopause was 38% but none in the postmenopause. This contrasting difference between the premenopause and postmenopause could be explained in terms of estrogen functioning apparatus.

PR is believed to be the product of estradiol action. Therefore, PR contents should be highly correlated with E₂R contents, if estradiol functioning apparatus was normal. This assumption was also proven in the present study of the correlation between E₂R and PR contents of the normal cervical tissues in the premenopause (Fig. 4) but such a relationship was not observed in the postmenopause. This results suggested that the estradiol functioning apparatus has been affected in the postmenopause, namely modification or inactivation of the system.

In support of the above assumption, there were several compatible reports; Strathy *et al.* (1982) found that E₂R in the postmenopausal endometrial tissue could not be translocated into the nucleus, and Pellikka *et al.* (1983) elucidated the structural difference between the receptors in the premenopause and postmenopause, probably due to proteolytic modification. Although these data were from the endometrial tissues indicating the functional inactiveness of E₂R in the postmenopause,

this explanation would be undoubtedly extended to the system in the cervix. And the relatively high level of E₂R without concomitant high level of PR in the postmenopausal cervix could be explained by the observation that E₂R in the postmenopause are mostly unoccupied, probably due to low level of endogenous estradiol in addition to their inactiveness (Saez *et al.* 1978; Gao *et al.* 1983). From these studies, it is evident that for the purpose of verifying estradiol mechanism, simultaneous measurement of E₂R and PR contents is important and that PR content is better index for estradiol function in the target tissue.

Concerning the effect of gravidity and parity on the receptor contents, none of the previous studies could be traced. In the present study, no apparent tendency was observed except significant decrease in E₂R contents in the group of parity of more than 5. But definite conclusion could not be drawn due to small sample size and it would be desirable to continue this kind of study.

The variation of E₂R and PR contents in the cervical tissues according to the cancerous changes is very important in the aspect of therapeutic and prognostic evaluation of cervical carcinoma. Since the results from breast cancer (Jensen *et al.* 1962; McGuire 1973; McGuire *et al.* 1973; Skinner *et al.* 1980) and endometrial cancer (Kistner *et al.* 1965; Reifsten *et al.* 1971; Young *et al.* 1976; Creasman *et al.* 1980; Hoffman and Siiteri, 1980; Kauppila *et al.* 1982) indicated that the effectiveness of hormone therapy was associated with better prognosis in the receptor positive cases. This concept might be extended to the cervical carcinoma in so far as the cervix is an estradiol-dependent organ.

However, up to now, in contrast to breast and endometrial carcinoma, cervical carcinoma has not been traditionally perceived as a hormonally responsive disease (Gao *et al.* 1983) and actually there has been no successive result on the hormonal therapy for cervical carcinoma and the research on the cervix was scanty. Bloch (1979) suggested that E₂R and PR contents increased with the progressive dedifferentiation of the cervical squamous epithelium and thereby hormone therapy on cervical carcinoma could be effective. And some reported that cervical cancer tissues had detectable E₂R contents (Terenius *et al.* 1971), more positive E₂R cases in the adenocarcinoma than squamous cell type (Hahnel *et al.* 1979), and positive rate of E₂R and PR in about one half of the cervical carcinoma (Gao *et al.* 1983). Some stu-

dies argued that the contamination of the tumor sample with the normal surrounding tissue could cast a doubt on the receptor contents, but the further histologic analysis proved the majority of the sample being tumor cells, so that the evident positivity of receptor in the tumor specimen could be explained (Soutter *et al.* 1981).

The result of the present study on the receptor contents of cervical carcinoma revealed that the carcinoma had considerably high level of E₂R and PR and showed some variation of receptor contents with histopathologic differences. In an effort to find out the correlation between the receptor contents and the clinicopathologic status of the cervical carcinoma, E₂R and PR contents were compared in relation to clinical stage, cell type, nuclear grade, mitotic rate, and lymphoid infiltration.

However, with advancement of clinical stage E₂R and PR contents did not exhibit any relationship (Table 7) in contrast to the debatable results of others who observed no relation (Creasman *et al.* 1980) and decrease in receptor contents with clinical advancement (Kauppila *et al.* 1982; Gao *et al.* 1983).

As shown in Table 8, E₂R and PR contents were higher in the non-keratinizing epidermoid carcinoma which suggests that keratinization of the tumor might have exerted reducing effect on the receptor contents. In general, the large cell non-keratinizing epidermoid cervical carcinoma was expected to have better prognosis and more common incidence (Fink and Denk 1970; Swan and Roddick 1973; Beecham *et al.* 1978) than keratinizing or small cell type.

The relationship of histopathologic parameters with E₂R and PR contents in the gynecologic malignancies have been thoroughly studied in endometrial as well as breast cancer (McCarty *et al.* 1980; Kim *et al.* 1982; Zaino *et al.* 1983), which could be summarized as the advancement of dedifferentiation such as increasing mitotic rate and nuclear grade lowered the receptor contents. However, such reports were scanty in cases of cervical carcinoma. The present study showed no significant changes of receptor contents in relation to nuclear grade, mitotic rate, and lymphoid infiltration. Other reports revealed decrease in PR contents with increasing dedifferentiation (McCarty *et al.* 1980; Kim *et al.* 1982) and Van Naegell *et al.* (1978) related receptor contents with lymphoid infiltration which might extend the speculation to the immunologic response of the tumor. It would be worthwhile to

continue the research on this relationship.

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= 국문초록 =

자궁경부의 정상 및 암조직에서 에스트라디올 및 프로제스테론 수용체에 관한 연구

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박찬용 · 신면우 · 박인서 *

자궁경부의 정상 및 암조직중 estradiol 및 progesterone 수용체 농도의 변화 양상을 검토해 본 결과는 아래와 같이 요약될 수 있다.

1. 월경기 여성에서는 estradiol 수용체의 농도는 분비기에서 증식기보다 유의하게 높았으나 progesterone 수용체의 농도는 큰 차이가 없었으며 폐경기에서 progesterone 수용체의 농도는 정상 월경기보다 낮은 경향을 보였다. 한편 estradiol 및 progesterone 수용체가 공히 양성인 분활은 월경기에서는 38%이었으나 폐경기에서는 전무하였다.
2. 임신 또는 분만 횟수에 따른 정상 자궁 경부의 estradiol 및 progesterone 수용체는 특별한 차이를 보이지 않았으나 분만 5회 이상의 군에서는 estradiol 수용체의 농도가 유의하게 낮았다.
3. 자궁경부조직중의 estradiol 및 progesterone 수용체 농도상호간의 관계는 월경기에서는 정의 유의한 상관도를 보인 반면 폐경기에서는 이러한 관계가 성립되지 않았다.
4. 정상 자궁경부조직에서 암세포로 진전에 따른 estradiol 및 progesterone 수용체농도의 변화는 보이지 않았다.
5. 자궁 경부암의 non-keratinizing type의 경우 keratinizing type보다 progesterone 수용체의 농도가 유의하게 높았으나 estradiol 수용체의 농도는 유의한 차이가 없었다.
6. 자궁 경부암의 기별, 핵분화도, mitotic rate, 임파구 침윤도에 따른 estradiol 및 progesterone 수용체의 농도는 유의한 차이가 없었다.