

# Epidermal growth factor receptor expression: is it the same in normal and malignant endometria?

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*Summary:* Epidermal growth factor was investigated in normal and malignant tissues in order to detect possible differences in its expression.

We used immunohistochemical techniques that employ murine monoclonal antibody 528. Thirty-nine patients (12 with normal endometria and 27 with endometrial adenocarcinomas) were examined. Epidermal growth factor receptor was seen in all normal uteri and in 27 uteri with adenocarcinoma. It was absent in 11 patients with cancer.

No correlation was found between the intensity of immunohistochemical staining and histologic grade, depth of myometrial invasion and clinical stage.

*Key words:* Epidermal growth factor; Endometrial cancer.

## INTRODUCTION

Epidermal growth factor (EGF) was first isolated by Cohen in 1962. Its effects depend on interaction with a specific cell membrane receptor, which is widely distributed in normal human tissues. It has been demonstrated in vitro that, after binding to its receptor, EGF acts as a mitogen for many cells <sup>(1)</sup>, suggesting that EGF may participate in processes of growth and differentiation in vivo. In

view of this finding, an increasing number of cancers have been investigated to find out if malignant transformation is associated with increased EGF expression.

Indeed, EGF receptor expression appears greatly increased in squamous cell cancers <sup>(2)</sup>, whereas it is demonstrable only in a proportion of adenocarcinomas <sup>(3, 4, 5)</sup>.

Mukku and co-workers <sup>(6)</sup> have shown that 17-beta-estradiol induces increased binding of EGF to uterine membranes from immature female rats; this result may suggest a role for EGF in normal and perhaps in abnormal proliferation of the uterus.

The aim of the present study was to immunohistochemically detect EGF receptor in normal and malignant endometria.

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## MATERIALS AND METHODS

Uterine tissues were obtained from 66 patients who underwent hysterectomy (39 for the treatment of benign gynecologic diseases and 27 for endometrial adenocarcinoma) (tab. 1).

Among the patients with benign diseases, 8 underwent hysterectomy for metrorrhagia, 2 for post-delivery hemorrhage and as many for multiple fibromyomas. Every time tissue samples were frozen in liquid nitrogen until an adequate amount of samples was available.

The mean age of the patients with endometrial cancer was 59 years. Fourteen of them had been examined by us for loss of blood, 5 for leucorrhoea, 1 for pelvic pain and 7 for routine gynecologic check-ups.

The patients were subjected to gynecologic examination, Pap-test and echotomography. For histological examination the tissues were taken by scraping during hysteroscopy. For clinical staging before operation, the patients underwent echography of the liver and kidneys, X-rays of the thorax, and, when possible, lymphography.

All 27 patients underwent hysterectomy by laparotomy, bilateral salpingo-oophorectomy and lymphadenectomy. Pelvic peritoneal cytologic testing was performed in 11 patients: in 6 patients with obvious advanced extrauterine disease, and in 5 patients with poor medical conditions.

According to the criteria outlined in the FIGO staging system, 18 patients had stage I, 3 patients had stage II, 4 patients had stage III and 2 patients stage IV.

When an adequate amount of samples was available, cryostat sections were mounted, and then incubated in phosphate-buffered saline solution with 0.3% hydrogen peroxide to neutralize endogenous peroxidase. After fixation, immunohistochemical staining was performed employing murine monoclonal antibody (MAB 528), which is specific for the external domain of the EGF receptor.

Table 1. — *Samples examined.*

Disease	No. of patients	Age	Treatment
Refractory metrorrhagia	8	45-56	Hysterectomy
Post-delivery haemorrhage	2	34-38	Hysterectomy
Multiple fibromyomas	2	40-44	Hysterectomy
Endometrial adenocarcinoma	27	56-63	Hysterectomy with bilateral salpingo-oophorectomy

## RESULTS

The intensity of staining was judged as absent, light, or heavy. EGF receptor was seen in all 12 normal uteri. Staining of endometrial glands and endometrial stromal cells was heavier, although staining was seen in all cellular elements. In each specimen, there was a homogeneous intensity of staining of all cells of each type. Homogeneous staining, instead, was not observed in slides from different patients but with endometria at the same functional stage. In uteri with endometrial cancer the results were different: EGF receptor was found only in 16 patients, while in the remaining 11 immunohistochemical staining was absent. In addition, no correlation was found between intensity of immunohistochemical staining and clinical stage, histologic grade, and depth of myometrial invasion (Table 2.).

Table 2. — *Relationship of EGF receptor expression to stage of endometrial adenocarcinoma.*

EGF receptor	Stage of tumor			
	I	II	III	IV
Present	10 (55%)	2 (66.6%)	3 (75%)	1 (50%)
Absent	8 (45%)	1 (33.4%)	1 (25%)	1 (50%)
Total	18	3	4	2

## DISCUSSION AND CONCLUSION

Since it was isolated in 1962, a large number of investigations have been carried out on the physiologic role of EGF and its receptor <sup>(7, 1, 8)</sup>. In view of its mitogenic action in vitro, a role in cancer has been proposed for EGF. However, though EGF receptor is present in a number of cancers, changes in its expression do not appear to be associated with tumors of several organs.

More interesting results have been obtained in studying the correlation of EGF

receptor expression with histological, clinical and prognostic factors of tumors. It has been suggested that, in breast and bladder cancer, the absence of EGF receptor is associated with favourable clinical outcome <sup>(3, 10, 11)</sup>.

Studies in lung cancer have pointed out that tumors with EGF receptor over-expression have poor prognosis <sup>(12)</sup>. Recent investigations on ovarian adenocarcinoma seem to associate the absence of EGF receptor with favourable clinical outcome <sup>(5, 8)</sup>.

Studies of endometrial adenocarcinoma have shown no relationship between EGF receptor expression and prognostic factors. Indeed, in our study, immunohistochemically detectable EGF receptor was expressed by 100% of the normal endometrium and by only 59% of the endometrial adenocarcinomas. In 11 cases (40.7%) of endometrial cancer, EGF was absent. In addition no correlation of EGF receptor with histologic grade, progression of disease and prognosis of cancer was found.

Presently, though data are contrasting, numerous and significant alterations of EGF receptor expression have been detected in various human cancers. However, the relationships between these alterations and the factors regulating development and metastases of tumors remain unclear.

Additional studies by comparable techniques are needed to clarify whether EGF receptor can be considered a tumoral prognostic factor.

## REFERENCES

- 1) Carpenter G., Zendejaj J.G.: "Epidermal growth factor, its receptor, and related proteins". *Exp. Cell Res.*, 1986, 164, 1-10.
- 2) Ozanne B., Richards C.S., Hendler F. *et al.*: "Over-expression of the EGF receptor

- is a hallmark of squamous cell carcinomas". *J. Pathol.*, 1986, 149, 9-14.
- 3) Sainsbury J.R.C., Farndon J.R., Sherbet G.V. *et al.*: "Epidermal growth factor receptors and oestrogen receptors in human breast cancer". *Lancet*, 1985, 1, 364-6.
- 4) Sobol R.E., Astarita R.W., Hofeditz C. *et al.*: "Epidermal growth factor receptor expression in human lung carcinomas defined by a monoclonal antibody". *J.N.C.I.*, 1987, 79, 403-7.
- 5) Bauknecht T., Runge M., Schwall M. *et al.*: "Occurrence of epidermal growth factor receptors in human adnexal tumors and their prognostic value in advanced ovarian carcinomas". *Gynecol. Oncol.*, 1988, 29, 147-57.
- 6) Mukku V.R., Stancel G.M.: "Regulation of epidermal growth factor receptor by estrogen". *J. Biol. Chem.*, 1985, 260, 9820-4.
- 7) Todaro G.J., Fryling C., De Larco J.: "Transforming growth factors produced by certain human tumor cells: polypeptides that interact with epidermal growth factor receptors". *Proc. Natl. Acad. Sci.*, 1980, 77, 5258-62.
- 8) Berchuck A., Rodriguez G.V. *et al.*: "Epidermal growth factor receptor expression in normal ovarian epithelium and ovarian cancer". *Am. J. Obstet. Gynecol.*, 1991, 164, 669-74.
- 9) Adamson E.D., Ress A.R.: "Epidermal growth factor receptors". *Mol. Cell. Biochem.*, 1981, 34, 129-152.
- 10) Sainsbury J.R., Farndon J.R., Needham G.K. *et al.*: "EGF-receptor status as predictor of early recurrence and death from breast cancer". *Lancet*, 1987, 1, 1398-402.
- 11) Neal D.E., Sharples L., Smith K. *et al.*: "The epidermal growth factor receptor and the prognosis of bladder cancer". *Cancer*, 1990, 65, 1619-25.
- 12) Sobol R.E., Astarita R.W., Hofeditz C. *et al.*: "EGF-receptor expression in human lung carcinomas defined by a monoclonal antibody". *J.N.C.I.*, 1987, 79, 403-7.

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