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Research Article

A study of expression of estrogen and progesterone receptor, in atrophic, hyperplastic and malignant endometrial lesions, with emphasis on relationship with prognostic parameters

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ABSTRACT

Background: Aims of current study were to study the expression of estrogen receptor (ER) and progesterone receptor (PR) in atrophic, hyperplastic and malignant endometrial tissue, using immunohistochemical markers.
Methods: The study includes 100 cases of endometrial tissues (25 cases each of atrophic and hyperplastic endometria and 50 cases of endometrial carcinomas).
Results: In atrophic endometrial, 20 cases were ER and PR rich. 5 cases showed complete loss of hormone receptors (4 were type I and 1 type II). All the 25 cases of hyperplasias were ER and PR positive with varying H-score. The analysis of the hormone receptors in endometrial carcinomas, indicated that ER in 34 cases (68%) and of the PR in 38 cases (76%) were positive.
Conclusions: Majority of the asymptomatic postmenopausal atrophic and hyperplastic endometria, expressed ER and PR. The value of the statistical significance was equal for atrophic vs. carcinomas and also hyperplastic vs. carcinomas. Positive ER PR expression was significantly associated with grade I-II and stage IB tumours. The correlation of immunohistochemical findings with histologic grade and clinical stage could help in predicting biologic behaviour and planning treatment in patients who are diagnosed as having these tumors.

Keywords: Estrogen receptor, Progesterone receptor, Endometrial carcinoma, Hyperplasia and atrophic endometria

INTRODUCTION

Endometrial carcinoma is becoming the most common gynaecologic malignancy in women, worldwide and occurs in reproductive and postmenopausal women. It represents a major health concern because overall five-year survival rates have not improved in the last three decades.[1,2] In addition to prolonged estrogenic use (HRT), the reasons for this increased incidence of endometrial carcinoma are thought to be lesser parity, greater infertility and greater incidence of life style diseases like obesity, hypertension and diabetes.[1-3]

Estrogen receptors (ER) and progesterone receptors (PR) are two key regulators of proliferation and differentiation in uterine endometrium and other reproductive tissues and belong to the nuclear steroid receptor superfamily.

The expression and relationship of the two distinct ER and PR could be of essential clinical implications. The

knowledge of pattern of steroid receptors in endometrial tissue is of extreme importance, since it might start a new field in hormone therapy of endometrial cancer.

Therefore, the aim of the present study is the evaluation of the distribution patterns of ER-alpha and PR-A and B in atrophic, hyperplastic and malignant endometrial tissues.

Aims and objectives

The aims and objectives of the study were:

1) To study the expression of estrogen and progesterone receptors in atrophic endometrial tissues from hysterectomy specimens of prolapsed cases using immunohistochemical markers.

2) To study the expression of ER and PR in uninvolved endometrium adjacent to endometrial carcinoma, using immunohistochemical markers.

3) To study the expression of ER and PR in hyperplastic endometria using immunohistochemical markers.

4) To study the expression of ER and PR in malignant endometrial tissue, using immunohistochemical markers.

5) To evaluate the association of ER, PR expression between atrophic endometria and endometrial carcinomas, with statistical analysis.

6) To evaluate the association of ER, PR expression between hyperplastic endometria and endometrial carcinomas, with statistical analysis.

7) To assess the relationship of ER, PR status with other established prognostic parameters like grade and type.

8) To study the pattern of expression of ER-alpha and PR-A and B in various histological types of endometrial carcinomas.

METHODS

Place of study: Department of Pathology, Guntur Medical College, Guntur.

Tissue samples: Slides and paraffin embedded tissue of endometrium, from diagnostic curettage and hysterectomy cases, with diagnosis of endometrial carcinoma, hyperplasia and atrophic endometrium, retrieved from the archives of Department of Pathology, Guntur Medical College, Guntur, India from Jan 2006 to July 2012.

Number of cases: The material used in our study comprised 100 endometrial tissues, which include, 50 cases of endometrial carcinomas, 25 cases of endometrial hyperplasias and 25 cases of Atrophic endometria , collected from asymptomatic postmenopausal women undergoing hysterectomy for a prolapsed uterus. Also 10 cases of atrophic endometria, adjacent to endometrial carcinoma, are analysed.

Histopathology: The original H&E stained sections were reviewed. The diseased endometria were grouped into respective histologic subtypes.

25 cases of endometrial hyperplasias, included in the study, were categorised into the subtypes, as simple hyperplasias (13 cases), complex hyperplasias (4 cases) and complex atypical hyperplasias (8 cases).

50 cases of endometrial adenocarcinomas included in the study, were reviewed and categorised into histological types as - endometrioid type (42 cases with stage IB, 6 cases and IC 6 cases, including 10 cases of villoglandular subtype), serous type (5 cases), mucinous type (1 case) and adenocarcinoma with squamous differentiation (2 cases).

The grading of endometrial carcinomas was reaffirmed using the FIGO/WHO grading criteria.

The atrophic endometrial were grouped into three categories namely:[4] Type I: Atrophic and inactive - those deprived of functionalis or with cystically dilated glands (16 cases). Type II: Atrophic and weakly proliferative-those with proliferative type of endometrial glands (4 cases). Type III: Mixed forms - 5 cases.

Immunohistochemistry: Immunohistochemistry is performed using a combination of microwave oven heating and standard streptavidin- biotin- peroxidase complex, using the Dako kit. Sections of human breast cancer tissue samples, were used for positive controls.

Briefly, paraffin embedded tissues were cut as 3-4 microns thick sections, dewaxed using two changes of xylol, each for 15 min, rehydrated in graded alcohols and subjected to antigen retrieval with microwave in citrate buffer (pH 6.0). After cooling, the slides were washed with phosphate buffer (pH 7). Endogenous peroxidase activity was quenched by immersion in 3% hydrogen peroxide. Sections are then incubated at room temperature for 60 min with primary antibodies ER-alpha and PR-A and B. After washing with phosphate buffer, the slides were incubated in diluted biotinylated serum for another 30 min at room temperature. After incubation with the avidin-biotin peroxidase complex for a further 30 min and a repeated washing step with phosphate buffer, visualization was performed with substrate and chromogen 3’3-diaminobenzidine for 8-10 min. The slides were further counter stained with Harris hematoxylin and washed in running tap water. After xylol

treatment, the slides were covered. Positive cells showed a brownish nuclear staining.

Evaluation and statistical analysis

The intensity and distribution of specific immunohistochemical staining reaction was evaluated using a semi quantitative method, i.e.; H-score.[6]

The H-score was calculated for 2s cases each of atrophic, hyperplastic and endometrial adenocarcinoma - endometrioid type. In the endometrioid variants, 15 grade I tumours, (14-stage IB, 1-stage IC) and 10 grade II tumors (7-stage IB, 3-stage IC) were included for statistical analysis.

Other histological subtypes like serous, mucinous and adenocarcinoma with squamous differentiation were excluded for statistical analysis.

The H-score was calculated as follows:[5]

3 times the % of strongly stained nuclei + 2 times the % of moderately stained nuclei + % of weakly stained nuclei. Score range is between 0 -300.

P value was calculated using chi square test to assess the correlation between atrophic and endometrial adenocarcinoma and between hyperplastic and endometrial adenocarcinoma.

RESULTS

A total of 100 endometrial tissues are included in study, of which 50 cases are endometrial adenocarcinomas, 25 cases are endometrial hyperplasias and 25 cases are atrophic endometria.

Clinical evaluation

Age evaluation

The mean age of the patients in the present study was 59 years (range 30-70 years).

In the present study majority of the endometrial hyperplasias were seen between 40-49 years, constituting (n=10; 40%).

Atrophic endometria were seen mostly above 50 years constituting (n= 22; 88%) and the age group with peak incidence of endometrial adenocarcinoma is between 50-59 years (n=36; 78%).

Histopathological evaluation

In this study hyperplastic endometria derived from diagnostic curettage specimens, were 25 cases, of which 13 were simple hyperplasia without atypia and 4 were complex hyperplasia without atypia and 8 cases were complex atypical hyperplasias.

The asymptomatic disease free postmenopausal endometria derived from prolapsed uterus were 25 cases, of which 16 were atrophic and inactive (Type I), 4 atrophic and weakly proliferative (TypeII), and 5 were of mixed form (Type III).

The non-neoplastic endometrium adjacent to endometrial adenocarcinoma was identified in 10 cases, out of total 50.

In this study, histopathological analysis of a total of 50 cases of endometrial carcinomas, 33 cases (66%) are Grade I, which include 22 cases endometrioid type, 10 villoglandular subtype and 1 mucinous type. 6 cases (12%) were Grade II, all of which were endometrioid type. 11 cases (22%) were Grade III tumors, of which 4 were endometrioid type, 5 were serous type and 2 were adenocarcinoma with squamous differentiation.

The myometrial invasion was limited to internal half of the thickness of myometrium in 21 cases and the invasion was present in outer half, reaching the serosa in 6 cases. Remaining 19 cases were curettage specimens only. Two cases were in Stage II and two cases in stage IV.

Vascular space invasion was present in 4 cases, associated with grade II and grade III tumors.

Immunohistochemical evaluation

In atrophic endometrial 20 cases were ER and PR rich. 5 cases showed complete loss of hormone receptors (4 were type I and 1 type II).

All the 25 cases of hyperplasias were ER and PR positive with varying H-score.

The analysis of the hormone receptors in endometrial carcinomas, indicated that ER in 34 cases (68%) and of the PR in 38 cases (76%) were positive.

The negative cases for both the receptors corresponded to Grade II (1 case) and Grade III (11cases) which include, all the 5 cases of serous carcinomas and 2 cases of adenocarcinoma with squamous differentiation.

Statistical evaluation

Semi quantitative grading of ER, PR expression is calculated by the H-score, for 25 cases each of atrophic, hyperplastic, and endometrial carcinomas and the mean value is calculated.

The association between ER, PR expression of hyperplastic endometria and endometrial carcinoma and between atrophic endometria and endometrial carcinoma

is done using Chi square test and P value obtained (Table 1, 2, 3 & 4).

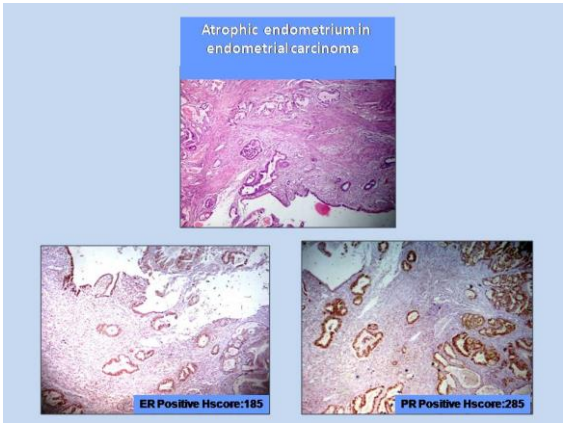

Figure 1: Showing Type I, II and III atrophic endometria (H & E, x10) with respective immunohistochemical expressions of estrogen and progesterone receptors and corresponding H-scores.

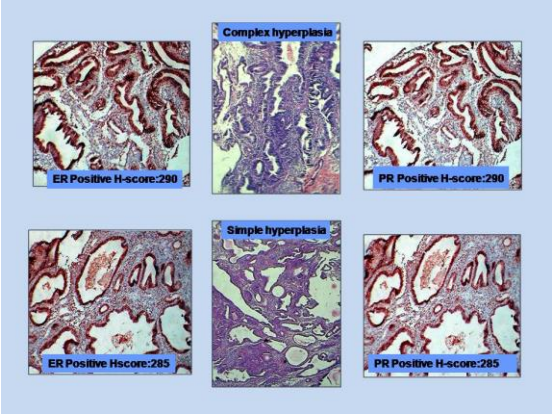

Figure 2: Showing endometrial adenocarcinoma, with adjacent atrophic endometrium (H & E, x10) with respective expression of estrogen and progesterone receptors and corresponding H-scores.

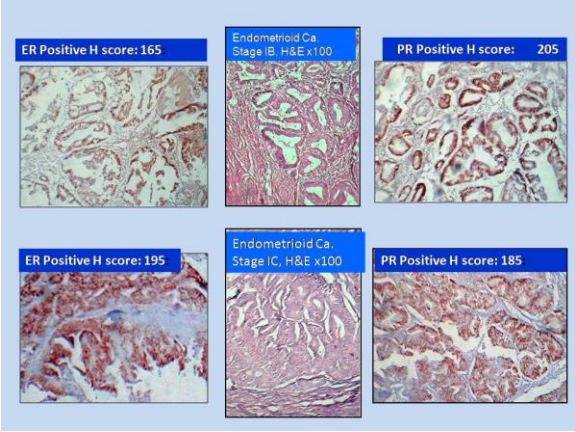

Figure 3: Showing simple and complex endometrial hyperplasias (H & E, x10) with respective immunohistochemical expression of ER and PR and corresponding H-scores.

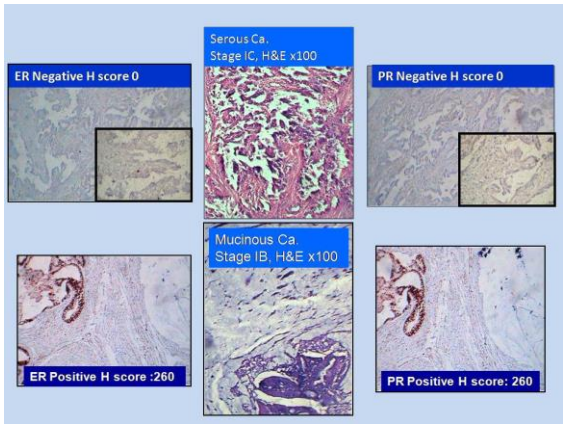

Figure 4: Showing endometrial adenocarcinoma-endometrioid type, in stage IB and IC (H & E, x10) with respective immunohistochemical expressions of ER and PR and corresponding H-scores.

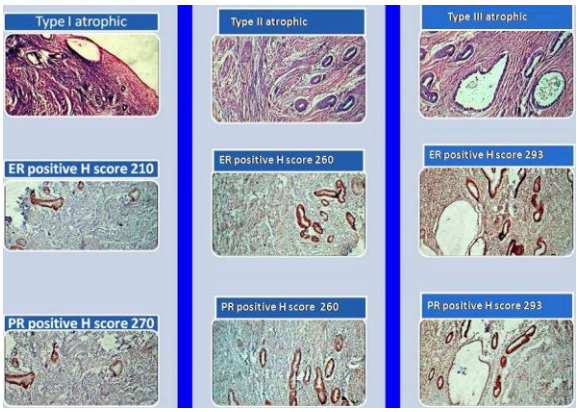

Figure 5: Showing serous and mucinous variants of endometrial adenocarcinoma, (H & E, x10) with respective immunohistochemical expressions of ER and PR and corresponding H-scores.

Table 1: Comparison of ER staining (H-scores) between atrophic endometria and adenocarcinoma.

ER	Atrophic	Adenocarcinoma
Mean of H-score	185.52	55.6
Chi square	668.39	
P value	0.0001 (less than 0.05)	

Table 2: Comparison of PR staining (H-score) between atrophic endometria and adenocarcinoma.

PR	Atrophic endometrium	Adenocarcinoma
Mean of H-score	180.72	177.4
Chi square	77.72	
P value	0.001 (less than 0.05)	

Table 3: Comparison of ER staining (H-scores) between hyperplasia and adenocarcinoma.

ER	Hyperplasia	Adenocarcinoma
Mean of H-score	169.2	55.6
Chi square	526.84	
P value	0.0001 (less than 0.05)	

Table 4: Comparison of PR staining (H-Scores) between hyperplasia and adenocarcinoma.

PR	Hyperplasia	Adenocarcinoma
Mean of H-score	208	177.4
Chi square	293.44	
P value	0.0001 (less than 0.05)	

In all the four categories, a significant p value of less than 0.05 was obtained.

DISCUSSION

The endometrium is a tissue of continuously changing patterns and of immense proliferative activity during women's reproductive life.

The ER and PR expression and distribution patterns play an important role in the normal endometrial function and tumorigenesis.

Both the ER and the PR have two subtypes: ER –alpha and beta and PR A and B, respectively. These subtypes differ in function and expression. The novel receptor ER-beta has a high homology (approx.95%) in the DNA binding domain, but only 55% homology in ligand binding domain, compared to the classical ER-alpha. ER-alpha can bind estradiol with a high affinity and react with a consensus Estrogen Response Element (ERE), stimulating transcription of ER target genes. The two isoforms of PR, PR-A and PR-B are generated by alternative transcription and translation from the same genes; the aminoacid sequences are identical except that PR-B has a longer N-terminus consisting of 164 aminoacids not present in PR-A.[6]

Association between atrophic and malignant endometria, with ER PR as parameters

Endometrium becomes atrophic after the menopause as a result of ovarian failure. At this time there is loss of functional layer and the endometrial glands take a simple tubular , often cystic form, showing neither proliferative nor secretory activity, whereas the endometrial stroma turns fibrous.[7] The Atrophic endometria can be grouped into three categories namely Type I: Atrophic and inactive- those deprived of functionalis or with cystically dilated glands. Type II: Atrophic and weakly proliferative- those with proliferative type of endometrial glands. Type III: Mixed forms.[4]

In a study by Sivridis, et al.[4] on 84 cases of atrophic endometrium, more than half of the atrophic disease free, symptom free, postmenopausal endometrium, exhibited weak proliferative activity. They observed a high ER and PR expression in both active and inactive endometria, but former were EGFR positive and had high proliferative Ki67 and angiogenic activity. A similar trend was also shown by the non-neoplastic atrophic endometrium, adjacent to endometrial carcinoma. Earlier Archer and colleagues[8] and Korhonem et al.[9] investigating endometrial patterns in asymptomatic postmenopausal women, found a similar proliferative activity in approximately 25% of the cases studied and hyperplastic disease is less than 5%. Although all postmenopausal endometria, whether active or inactive , retain full ER and PR complement, as shown in the some studies, only those showing a weak proliferative activity, which are EGFR positive and with a high angiogenic and proliferative (Ki-67) activity, show a low potential for giving rise to endometrial adenocarcinoma.[10]

Endometrial cancer is made up of a biologically and histologically diverse group of neoplasms that are characterized by a different pathogenesis. Estrogen dependent tumors (type I) are low grade and frequently associated with endometrial hyperplasias, in particular atypical hyperplasia. Unopposed estrogenic stimulation is the driving force behind this group of tumors. The second type (type II) of endometrial cancer appears less related to sustained estrogenic stimulation.[11] Historically, estrogen has been seen as a direct promoter of endometrial carcinogenesis. The estrogen, on the one hand, can bind to nuclear ER, causing stimulation of rapid proliferation of epithelial cells, and on the other hand, can increase the rate of mutations. [12, 13].But only 15-20% of endometrial carcinomas arise from a hyperplastic endometrium, the risk of progression from simple endometrial hyperplasia being very low (0.3-1%).[14-17] So majority of endometrial carcinomas are type II, which arise from a background of atrophy.

In the present study 25 cases of, disease free, symptom free, postmenopausal atrophic endometria and 10 cases of atrophic endometria, adjacent to endometrial carcinoma were analysed. Only 4 cases of disease free, atrophic endometria were negative for ER PR receptor status.

Also the statistical analysis (Tables 1, 2) done using H-Scores, to assess the relation between atrophic and malignant endometria showed a p value of less than 0.05, suggesting that endometrial adenocarcinomas related to endometrial atrophy (as most of these tumors are) originate from weakly proliferating glands and not from a back ground of endometrial inertia. Thus, these tissues have a latent, although very small, carcinogenic potential.

Association between hyperplastic and malignant endometria, with ER PR as parameters

Hyperplasia is a non-physiological and non-invasive proliferation at the endometrium level. There are two forms of hyperplasia: the atypical form representing a precursor lesion to endometrial adenocarcinoma, and the non-atypical form, which is a self-limiting increase, and does not seem to lead to cancer.[17]

Though the mechanism of progression from hyperplasia to endometrial carcinoma has not been fully elucidated, evaluation of immunohistochemical preparations showed that the ER alpha and PR- A and B expression in the endometrium were closely related to endogenous hormone stimulation and hyperplastic changes in the endometrium.

Nyholm et al. and Bergeron et al. reported that ER and PR levels were high in the epithelium of simple and complex hyperplasia and low in simple hyperplasia with atypia and complex hyperplasia with atypia and much lower in adenocarcinoma.[18,19]

In the current study, ER-alpha and PR-AB were expressed in all the 25 cases of endometrial hyperplasias, which included simple and complex hyperplasia without cytological atypia and complex hyperplasia with cytological atypia. These observations are in accordance with the above studies.

Also statistical analysis of the present study results (Table 3, 4), to determine the relationship between H-scores of hyperplastic endometria and endometrial carcinomas, showed a significant P value of less than 0.05, hence reaffirming the role of estrogen in hyperplasias and carcinomas.

ER PR expression, in endometrial carcinomas - the relationship with prognostic parameters

The endometrial carcinoma is one of the malignant tumor lesions, for which there are histopathological parameters that have definite prognostic value. Thus, numerous studies in the literature consider the stage and histopathologic tumor grade as being the most relevant feature for subsequent therapeutic management.[20,21]

Other studies have assigned the depth of the myometrial invasion and the vascular invasion as being prognostic parameters in terms of survival and recurrence rate of the endometrial carcinomas.[22,23]

The hormone receptor state, alongside with the histopathological features in the tumor tissue are important prognostic factors. Data from literature indicates the positivity for ER and PR in 35 to 90 % of endometrial carcinomas.[24]

And there exist a significant correlation between the estrogen and the progesterone receptor status and the staging of the endometrial cancer.[25]

The Grade I tumors are more frequently positive for the estrogen and the progesterone receptors than the poorly differentiated lesions.[26]

In the present study, the ER and PR expressions were positive in 79% and 88.37% respectively, of the analysed endometrial carcinoma cases.

The positivity index values for estrogen and progesterone decreased with the increasing grade, with the myometrial invasion and the stage of the tumor, which correspond with the literature. For the stage I endometrial cancers 66.6 % of cases are ER and PR positive, for the 2 cases of stage II endometrial cancers, ER and PR were positive and for stage IV endometrial cancers, ER and PR were negative.

In the present study, Grade I endometrial carcinomas, corresponded to stage I, compared with the Grade II or Grade III in advanced stages.

ER and PR expression, in the histological variants of endometrial carcinomas

Some studies show that both ER and PR were more often positive in endometrioid than in serous tumors which indicate that there exist different molecular pathways of tumorigenesis.[27,28]

In the present study also, all the five cases of serous carcinomas which were analysed, were ER and PR negative (Figure 5). Hence, it suggests that the immunohistochemical analysis of endometrial carcinoma differentiates between different grades and histological types, thus being useful in the distinction of high risk cases.

Mucinous carcinoma is an uncommon type of all endometrial cancer. It represents about 1 to 9 % of all endometrial carcinomas. Most are low grade and have a relatively good prognosis. There is positive expression of ER and PR in mucinous carcinoma.[29]

In the present study, 1 case of mucinous endometrial carcinoma was analysed for ER, PR expression and showed strong positivity, which corresponds with literature (Figure 5).

CONCLUSIONS

Majority of the asymptomatic postmenopausal atrophic endometria, expressed ER and PR.

The non-neoplastic endometrial glands adjacent to malignant tissues also exhibited analogous immunohistochemical profile, being ER and PR rich.

Majority of the hyperplastic endometria, with and without atypia, expressed ER and PR.

The value of the statistical significance was equal for atrophic vs. carcinomas and also hyperplastic vs. carcinomas.

All endometrioid adenocarcinomas, whether hyperplasia or atrophy related, are estrogen dependant and have only varying degrees of hormonal dependence this being high in case of hyperplasia and low, and perhaps of longer duration, in endometrial atrophy.

Although all postmenopausal endometria, whether active or inactive, retain full ER and PR complement, which are EGFR positive and with a high angiogenic and proliferative (Ki-67) activity, show a low potential for giving rise to endometrial adenocarcinoma.

Positive ER PR expression was significantly associated with grade I-II and stage IB tumours.

The correlation of immunohistochemical findings with histologic grade and clinical stage could help in predicting biologic behaviour and planning treatment in patients who are diagnosed as having these tumors.

Increased intensity of PR than ER expression, was linked with endometrioid histology.

Grade III carcinomas, serous and adenocarcinomas with squamous differentiation were ER and PR negative.

Mucinous carcinoma of endometrium is a rare histological variant, considered to be of low grade and expressed strong ER and PR positivity.

This study provides that the immunohistochemical analysis of endometrial carcinoma differentiates between different grades and histological types, thus being useful in the distinction of high risk cases.

The differences in immunohistochemical profiles of endometrioid and serous carcinomas support the existence of different molecular pathways of their development.

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