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ASSOCIATION OF ESTROGEN AND PROGESTERONE RECEPTOR STATUS AND METABOLIC HORMONES WITH TUMOR PROGRESSION IN ENDOMETRIAL CANCER

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Background. *It is recognized that endometrial physiology and carcinogenesis depend on the balance of estrogen and progesterone. Expression status of estrogen (ER) and progesterone (PR) receptors has been utilized clinically as a prognostic predictor of endometrial cancer (EC). Nevertheless there is growing evidence that insulin resistance and changes in adipokine secretory system are also important risk factor of EC.* ***Objective.*** *To investigate the association between tumor estrogen and progesterone receptors expression combined with metabolic hormone serum levels and tumor progression in patients with endometrial cancer.* ***Methods.*** *The study included 100 patients with endometrial cancer patients and 50 age-matched healthy controls. Serum estradiol, progesterone, insulin, leptin and adiponectin were analyzed with a chemiluminescent immunoassay. Tumor tissue samples were stained using monoclonal antibodies against ER and PR with a standard streptavidin-biotin method. Nuclear staining ≥10% was considered positive.* ***Results.*** *It was shown that the majority of the tumors were ER-positive (68%) and PR-positive (54%) while 27% were double-negative. Serum estradiol, leptin, and insulin levels were significantly higher in advanced-stage patients, while progesterone and adiponectin levels were significantly lower compared to early-stage patients. Correlation and regression results showed that the independent variables that predicted tumor progression were ER and PR negativity, high estradiol, high leptin, and low adiponectin.* ***Conclusions.*** *The loss of ER/PR expression and a metabolic hormonal imbalance – characterized by elevated levels of estradiol and leptin and reduced levels of adiponectin – are closely associated with the progression of endometrial cancer. These changes may contribute to proliferative signaling pathways and inflammatory processes, leading to increased tumor aggressiveness and disease progression.*

K e y w o r d s: endometrial cancer, estrogen receptor, progesterone receptor, monoclonal antibodies, leptin, adiponectin, insulin.

The most prevalent gynecological malignancy in developed and developing countries is endometrial cancer (EC), the incidence of which has steadily increased, partly due to the increasing number of obese people, metabolic syndrome and aging of populations [1]. The disease is conventionally categorized in terms of estrogen-dependent (Type I) and non-estrogen-dependent (Type II), with the former type of tumor being prevalent. The tumors are normally attributed to long-term exposure of unopposed estrogen, hyperplasia of the endometrium, and have good prognosis. Nevertheless, even with this classical dichotomic model, there is a significant variation in clinical outcomes across the same histological subtype, and more specific biological predictors of tumor progression are required [2].

The endometrial physiology and carcinogenesis depend on estrogen and progesterone receptors (ER and PR), which are the primary regulators. It

is reported that estrogen activates endometrial proliferation by stimulating genomic and non-genomic pathways such as PI3K/Akt and MAPK cascades, whereas progesterone inhibits estrogen-induced proliferation by inducing differentiation and apoptosis. In a normal endometrium, these hormones have a fine balance which maintains cyclic regeneration and shedding. Disturbance of this ratio, especially the long-term stimulation of estrogen without sufficient progesterone cues, induces a pro-proliferative microenvironment with preference to the malignant transformation [3]. ER and PR expression status has been largely utilized clinically as a prognostic predictor. ER and PR-positive tumors that are not lost in the process of tumor evolution are likely to have a well-differentiated histology, lower grade, and increased survival rates but receptor-negative tumors are more likely to have aggressive behavior and a less responsive reaction to hormonal therapy [4, 5].

Even though the receptor status contains useful prognostic data, it does not account completely to the heterogeneity that is found with disease progression. There is growing evidence indicating that metabolic and adipose-derived hormones play a critical role in modulating tumor biology. Chronic low-grade inflammation, insulin resistance, and changes in adipokine secretion of leptin and adiponectin are the major features of obesity as an important risk factor of EC [6, 7]. Leptin, which tends to be high in obese plays a pro-tumorigenic role by promoting cell proliferation, angiogenesis and anti-apoptotic signaling, including JAK/STAT3 and PI3K/Akt, in part. On the contrary, adiponectin has anti-inflammatory and anti-proliferative effects, and decreased levels of adiponectin have been recognized as risk and prognosis predictors of EC [8].

Besides adipokines, hyperinsulinemia and insulin resistance also contribute to endometrial carcinogenesis by increasing bioavailable estrogen and enhancing insulin-like growth factor (IGF) signaling pathways [9]. Insulin may also cause the growth of tumor cells directly and indirectly via aromatase activity in adipose tissue, which promotes the production of estrogens. High levels of estradiol in circulation, especially in postmenopausal women, have a close relationship with the development and progression of EC, which further supports the idea of estrogen dominance as a key pathogenic process [10].

Concomitant assessment of ER/PR condition and circulating hormonal and metabolic biomarkers might thus yield a more useful model of tumor behavior prediction. Although ER and PR mirror the sensitivity of intrinsic tumor to hormonal signaling, systemic surrogates of hormone signaling include estradiol, leptin, adiponectin and insulin, and reflect the overall metabolic milieu of cancer progression [11]. The combination of these parameters may enhance the stratification of risks, predict patients at greater risk of developing the advanced stage of the disease, and determine individual therapeutic approaches, such as hormonal therapy and metabolic interventions [12].

Although the metabolic–hormonal axis in endometrial cancer is increasingly recognized, limited studies have systematically explored the combined association of conventional receptor status with established hormonal and metabolic biomarkers. The dynamic interplay between receptor expression and systemic hormonal alterations may provide valuable insights into the synergistic mechanisms underlying tumor aggressiveness [13, 14]. Although these metabolic hormones have been individually associated with endometrial cancer risk and progression, few studies have evaluated their combined interaction with ER and PR status in a unified analytical model. Therefore, the present study focuses on investigating the integrated association of these established biomarkers to better understand tumor progression.

Materials and Methods

This case–control study was conducted between April 2025 and February 2026 to investigate the association between estrogen receptor (ER) and progesterone receptor (PR) status alongside selected metabolic hormonal biomarkers and tumor progression in patients with endometrial cancer. One hundred and fifty women were recruited comprising 100 patients who had just been diagnosed with endometrial carcinoma and 50 age-matched healthy controls. The patients were identified in the Gynecology Oncology Department and identified as having been diagnosed to clinical presentation (abnormal uterine bleeding), transvaginal ultrasonography, endometrial thickness measurement and confirmatory histopathology analysis post endometrial biopsy or hysterectomy specimens by WHO classification criteria. The FIGO staging system was applied in the determination of tumor staging. Women aged 40-75 years with histologically confirmed primary endometrial carcinoma without previous chemotherapy, radiotherapy, and hormonal therapies were also used as inclusion criteria. Other malignancies, chronic in-

flammatory or autoimmune diseases, severe hepatic or renal dysfunction, endocrine (other than obesity-related metabolic syndrome) or immunomodulatory drugs were excluded. Controls were seemingly healthy females with good gynecological checkup, who had no history of malignancy and chronic inflammatory illnesses. Aseptic venous blood samples (57 ml) were taken from the fasting participants. The samples were left to clot, centrifuged at 3000 rpm for 10 min, and serum aliquots were frozen at -80°C until analysis. The insulin, leptin, adiponectin, serum estradiol and serum progesterone were analyzed with a chemiluminescent immunoassay (CLIA) on an automated analyzer according to the instructions of the manufacturer. Each assay had internal quality controls. The tumor tissue samples were fixed in 10% neutral buffered formalin and then embedded in paraffin and cut into sections of 4 μm thickness. Formalin-fixed, paraffin-embedded tissue sections (4 μm) were stained using monoclonal antibodies against ER and PR with a standard streptavidin–biotin method. Nuclear staining ≥10% was considered positive. Slides were evaluated independently by two blinded pathologists. To ensure reproducibility, two senior pathologists evaluated all slides and were blinded to clinical information. Nuclear staining in ≥10% of tumor cells was considered positive for both ER and PR. Double positivity (ER+/PR+) was defined when both receptors met this cut-off within the same tumor sample, while double negativity (ER–/PR–) was defined when neither receptor reached this threshold.

Statistical analysis was performed using SPSS version 26.0 (IBM Corp., USA). Continuous variables were expressed as mean ± SD, and categorical variables as frequencies and percentages. Normality was assessed using the Kolmogorov–Smirnov test. Independent t-test and chi-square test were used for comparisons. Pearson correlation and multivariate logistic regression analyses were applied to assess associations and identify independent factors. A *P*-value < 0.05 was considered statistically significant.

Ethical approval. The study was approved by the Human Ethics Committee of Al-Imamain Alkadhimain Medical City (Protocol No 134-25, April 2025). Everyone who took part in the study was informed and asked to sign a consent form. The patient was also guaranteed that his information would be kept private.

Results

Comparison of demographic variables, metabolic risk factors, and tumor stage distribution between study groups. As shown in Table 1, BMI and diabetes mellitus were significantly higher in patients compared to controls ($P = 0.001$ and $P = 0.031$, respectively). No significant differences were observed in age, postmenopausal status, or hypertension ($P > 0.05$).

Frequency and percentage of ER and PR expression patterns among the studied cases (n = 100). As shown in Table 2, ER positivity (68%) was higher than PR positivity (54%), while ER negativity and PR negativity were observed in 32 and 46% of cases, respectively. Dual-positive tumors were more frequent (49%) than dual-negative tumors (27%), indicating variability in hormone receptor expression patterns among patients.

The presented images are representative examples illustrating strong positive and negative staining patterns; however, staining intensity varied among cases and was systematically evaluated across all samples (Figure).

Evaluation of reproductive and metabolic hormone levels in study groups. As shown in Table 3,

Table 1. Sociodemographic and clinical characteristics of endometrial cancer patients and healthy controls

Variable	Endometrial cancer, *n* = 100	Controls, *n* = 50	*P*-value
Age, years, mean ± SD	59.3 ± 8.7	56.8 ± 7.9	0.081
BMI, kg/m^2	31.2 ± 4.6	28.5 ± 3.9	0.001**
Postmenopausal, %	76 (76%)	32 (64%)	0.118
Diabetes Mellitus, %	38 (38%)	10 (20%)	0.031*
Hypertension, %	42 (42%)	14 (28%)	0.094
Stage I–II, %	61 (61%)	N/A	N/A
Stage III–IV, %	39 (39%)	N/A	N/A

Table 2. Distribution of estrogen and progesterone receptor status in endometrial cancer patients

Receptor status	Frequency, n = 100	Percentage
ER Positive	68	68%
ER Negative	32	32%
PR Positive	54	54%
PR Negative	46	46%
ER+/PR+	49	49%
ER-/PR-	27	27%

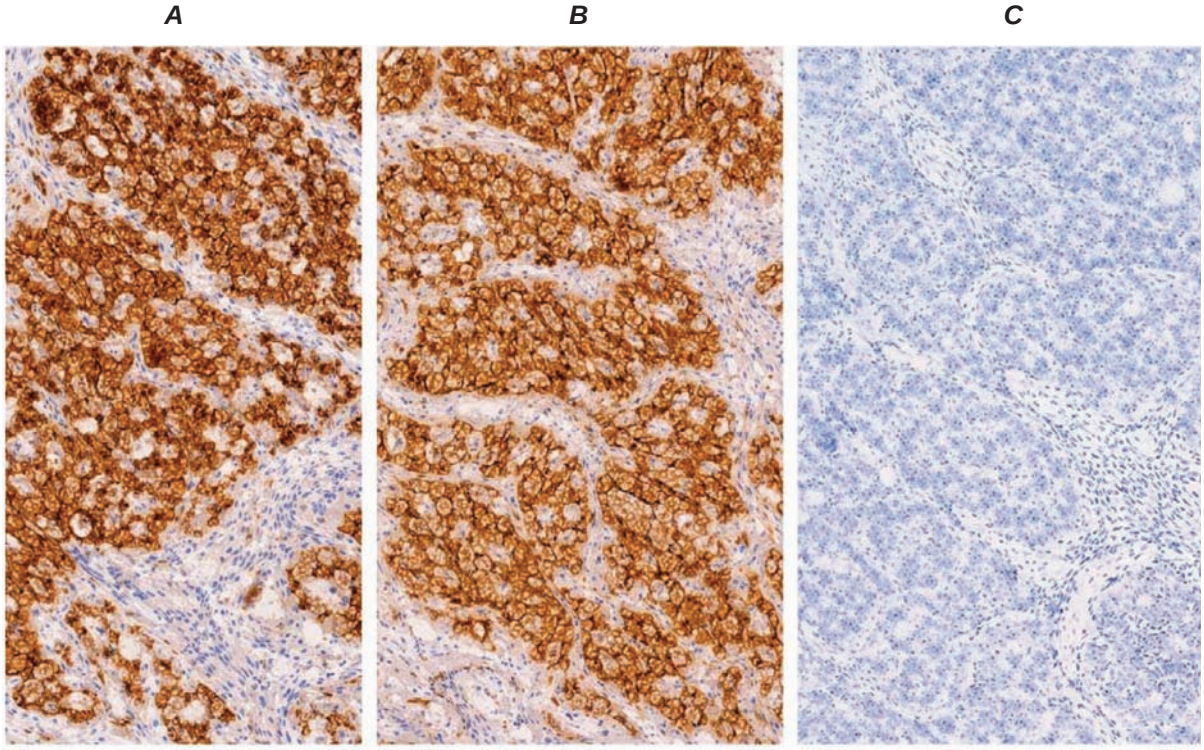

*Figure. Illustration samples of representative immunohistochemical staining on endometrial carcinoma tissue sections with a variety of patterns of hormone receptors expression. The estrogen receptor (ER) in panel (**A**) shows a strong positive nuclear stain in most of the malignant epithelial cells. Diffuse nuclear immunoreactivity and intense nuclear immunoreactivity with progesterone receptor (PR) is depicted in panel (**B**). Panel (**C**) is an ER/PR-negative tumor (no nuclear staining, only stained with hematoxylin). Immunostaining was done with monoclonal antibodies in a streptavidin-biotin detection system, and the positivity of the receptor was determined as nuclear staining in at least 10% of the tumor cells. Original magnification: ×400.*

estradiol, leptin, and insulin levels were significantly higher in patients, while progesterone and adiponectin levels were significantly lower compared to controls (all $P < 0.001$).

Comparison of reproductive and metabolic hormone levels between early-stage (I–II) and advanced-stage (III–IV) disease. As shown in Table 4, estradiol, leptin, and insulin levels were significantly higher in advanced-stage patients, while progesterone and adiponectin levels were significantly lower compared to early-stage patients ($P = 0.002$, $P = 0.005$, $P < 0.001$, $P < 0.001$, and $P = 0.001$, respectively).

Pearson correlation coefficients demonstrating interrelationships among estradiol, progesterone, leptin, and tumor stage. As shown in Table 5, es-

Table 3. Comparative serum hormonal profile between endometrial cancer patients and controls

Hormone	Patients (mean ± SD)	Controls (mean ± SD)	*P*-value
Estradiol, pg/ml	78.4 ± 24.6	52.2 ± 18.3	<0.001***
Progesterone, ng/ml	0.81 ± 0.39	1.34 ± 0.47	<0.001***
Leptin, ng/ml	36.5 ± 10.8	24.7 ± 8.9	<0.001***
Adiponectin, μg/ml	5.9 ± 1.8	8.6 ± 2.3	<0.001***
Insulin, μIU/ml	19.4 ± 6.7	12.8 ± 4.1	<0.001***

Table 4. Association between hormonal markers and tumor stage in endometrial cancer patients

Marker	Stage I–II (*n* = 61)	Stage III–IV (*n* = 39)	*P*-value
Estradiol	71.3 ± 20.5	89.6 ± 26.4	0.002**
Progesterone	0.92 ± 0.41	0.65 ± 0.33	0.005**
Leptin	31.8 ± 9.5	42.7 ± 11.4	<0.001***
Insulin	16.8 ± 5.2	23.5 ± 6.1	<0.001***
Adiponectin	6.5 ± 1.9	4.9 ± 1.4	0.001**

Table 5. Correlation matrix between hormonal markers and tumor stage in endometrial cancer

Variable	Estradiol	Progesterone	Leptin	Tumor stage
Estradiol	1	-0.54***	0.61***	0.48***
Progesterone	-0.54***	1	-0.42**	-0.46***
Leptin	0.61***	-0.42**	1	0.52***
Tumor stage	0.48***	-0.46***	0.52***	1

Table 6. Multivariate logistic regression analysis of factors associated with advanced endometrial cancer

Variable	OR	95% CI	*P*-value
ER Negative	2.74	1.28–5.86	0.009**
PR Negative	3.12	1.46–6.66	0.003**
High Estradiol	1.29	1.10–1.51	0.001**
High Leptin	1.34	1.15–1.57	<0.001***
Low Adiponectin	1.41	1.16–1.71	<0.001***
Diabetes	1.89	0.94–3.79	0.071

tradiol was negatively correlated with progesterone and positively correlated with leptin and tumor stage ($P < 0.001$). Progesterone showed negative correlations with leptin and tumor stage ($P = 0.01$ and $P = 0.001$), while tumor stage was positively correlated with leptin ($P < 0.001$).

Independent risk factors associated with tumor progression based on receptor status, hormonal profile, and metabolic variables. As shown in Table 6, ER and PR negativity, high estradiol, high leptin, and low adiponectin were significantly associated with tumor progression ($P = 0.009$, $P = 0.003$, $P = 0.001$, $P < 0.001$, and $P < 0.001$, respectively), while diabetes was not statistically significant ($P = 0.071$).

Discussion

The current research paper offers combined data that the development of endometrial cancer can be seen as a dynamic interplay between the traditional signaling via steroid hormones and metabolic-

inflammatory malregulation. The current study does not introduce new biomarkers; rather, it highlights the importance of integrating established hormonal and metabolic markers with receptor status to better characterize tumor progression. This combined approach may provide additional clinical value beyond evaluating each marker individually. There was no significant difference in age between the patients and the controls, suggesting that age was not a significant confounding factor in this cohort and further supporting the validity of the metabolic and hormonal differences.

On the contrary, the considerably increased BMI among patients can be compared to strong epidemiological statistics, which claim obesity to be one of the strongest risk factors that can be modified in relation to endometrial cancer. Numerous meta-analyses have shown that there is a dose-response relationship between the escalating body mass index and elevated risk of endometrial cancer, and this has been mainly attributed to peripheral aromatization of androgens to estrogens in the adipose tissue, reduced sex hormone-binding globulin (SHBG) and chronic low-grade inflammation [15, 16].

The fact that diabetes mellitus is much more common among patients is also an added support to the fact that has already been established, namely, that insulin resistance and endometrial carcinogenesis are closely related [17]. Hyperinsulinemia increases the bioavailable estrogen and changes the mitogenic pathways like PI3K/Akt and the IGF-1 signaling pathways, and stimulates the proliferation of the potent cells and suppresses the occurrence of apoptosis [18]. Though hypertension and postmenopausal status were more common in patients, this was not statistically significant and could be due to the study having a limited number of patients or the overlapping age effect or that their oncogenic effect is correlated with obesity and metabolic dysfunction rather than independent [19].

The receptor profile of this study, with the majority of tumors being ER positive and a significant number of tumors being PR positive, agrees with the classical concept that most endometrioid carcinomas are hormone-regulated. The presence of ER and PR expression in tumors is usually linked with improved differentiation and more promising results [20, 21]. On the other hand, the substantial percentage of ER-negative and PR-negative tumors, especially 27% of the double-negative ones, is of clinical importance, in that, in a number of studies, the loss of receptors was associated with increased grade, deeper myometrial invasion, lymphovascular space invasion, and worse prognosis [22, 23]. This phenomenon can be explained biologically by tumor dedifferentiation: during the development of malignancy, cancer cells can no longer rely on the action of steroid hormones and start to use growth factor-signaling pathways, such as the activation of HER2, MAPK, and PI3K/Akt. Nonetheless, not every study has discovered a robust correlation between loss of receptors and stage or survival [24, 25]. Methodological variations among studies could be due to discrepancies in immunohistochemical scoring systems, positivity cut-off points, inter- observer variability as well as the heterogeneity of tumor histological subtypes. Furthermore, in the situation of some inconsistent results, molecular classification (e.g., POLE-mutated, microsatellite instability-high, copy-number high) might superb the receptor-based prognostication [26].

The endocrine imbalance is the key factor in the pathogenesis of endometrial cancer, as further supported by the comparisons of the hormonal and metabolic profiles of patients versus controls. The presence of considerably high levels of estradiol and low levels of progesterone in patients indicates that the patients are under an unopposed exposure to estrogen, which is one of the prerequisites of type I endometrial carcinogenesis [27, 28]. Endometrial proliferation is stimulated by estrogen through the activation of ER-mediated transcription and PI3K/Akt and MAPK signaling, and inhibited by progesterone through differentiation and apoptotic stimulation. Lower concentrations of progesterone can thus increase the effects of estrogenic signaling and enhance the development of malignancy [30]. The same findings have also been noted in case-control and cohort studies, which have shown high levels of circulating estradiol in patients with endometrial cancer [31].

The metabolic hormone changes observed (increased levels of leptin and insulin and decreased levels of adiponectin) are also justified by the literature. Leptin, which is mainly produced by adipose tissue, has a pro-proliferative and pro-angiogenic action via JAK/STAT3, ERK, PI3K/Akt, and high levels of leptin were linked to elevated risk and aggressiveness of endometrial cancer [31]. On the other hand, adiponectin has anti-inflammatory and anti-proliferative effects that mediate through AMPK and mTOR signal inhibition; reduced adiponectin levels

in the blood have always been associated with an increased risk of endometrial cancer in meta-analyses [32]. The fact that patients had elevated insulin levels also supports the idea of metabolic hormonal synergy because hyperinsulinemia increases the bioavailability of estrogen and directly stimulates tumor growth through insulin receptor and IGF-1 receptor signaling [33]. However, other studies have found less significant or insignificant relationships between adipokines and the presence of tumors when corrected by the effect of BMI, indicating that some of their action could be caused by obesity itself. These differences can be due to ethnic variations, assay sensitivity differences, or models used that do or do not adjust the diluting metabolic variables [34].

It is worth noting that the tumor stage stratification revealed that the high-stage disease was associated with high levels of estradiol, leptin and insulin and low levels of progesterone and adiponectin. These findings are pointers to the fact that endocrine and metabolic disorders are simultaneously risk factors of the disease, and they can directly contribute to the development of tumors. The correlation analysis supported this interpretation: estradiol was found to have a positive relationship with leptin and tumor stage, but there was an inverse relationship between progesterone and leptin as well as tumor stage. The stage was also positively correlated with leptin, which means that leptin is involved in the promotion of tumor aggressiveness. These interactions suggest that there is an orchestrated biological system where estrogen pre-eminence and adipokine imbalance support each other in promoting proliferation and invasion. Other studies have also found similar hormonal patterns, stage-dependent and associated with the components of metabolic syndrome with high-grade endometrial cancer features [35, 36].

The independent study of receptor and metabolic markers as prognostic indicators provides a particularly strong argument in the multivariate logistic regression analysis. ER negativity and PR negativity had a great impact on advancing the disease. The results are consistent with prior research indicating that receptor loss prognosticates worse outcomes [37, 38]. Furthermore, high estradiol, high leptin, and low adiponectin did not lose their significance after the controls, which mean that the variables provide information on top of the conventional clinicopathological variables. Interestingly, the statistical significance was not maintained in diabetes in spite of a high odds ratio. This could indicate collinearity with the levels of insulin and adipokines, which are closer biological mediators of metabolic dysregulation. The independent effect of diabetes as a categorical diagnosis may go away once these variables are incorporated into the model [39].

Conclusion. Collectively, these findings suggest an integrated pathophysiological framework in which alterations in hormonal receptor status, estrogen dominance, and metabolic–inflammatory disturbances are associated with tumor characteristics in endometrial cancer. Variability among studies may be attributed to differences in methodology, molecular subtypes, and population characteristics. The combined assessment of ER/PR status with established metabolic hormonal biomarkers may provide additional insight into tumor behavior; however, further prospective studies are required to confirm their clinical applicability.

Author contributions. I. H. Ali conceptualized, methodologically designed, collected data and drafted the manuscript. S. M. Hasan participated in study design, supervision, data interpretation and critical revision of the manuscript. The laboratory investigations, statistical analysis and data validation was carried out by N. H. Khedhir. O. Mohsein participated in methodology, scientific review, editing and in approving the manuscript. The final version of the manuscript was read and approved by all the authors.

Conflict of interest. The authors have completed the Unified Conflicts of Interest form at http://ukrbiochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

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ЗВ'ЯЗОК СТАНУ РЕЦЕПТОРІВ ЕСТРОГЕНУ ТА ПРОГЕСТЕРОНУ В ПОЄДНАННІ З МЕТАБОЛІЧНИМИ ГОРМОНАМИ З ПРОГРЕСУВАННЯМ ПУХЛИНИ РАКУ ЕНДОМЕТРІЯ

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Вступ. Відомо, що фізіологія ендометрія та канцерогенез залежать від балансу естрогену та прогестерону. Статус експресії рецепторів естрогену (ER) та прогестерону (PR) використовується в клінічній практиці як прогностичний фактор раку ендометрія. Проте з'являється все більше доказів того, що інсулінорезистентність та зміни в системі секреції адипокінів також є важливими чинниками ризику розвитку раку ендометрія. **Мета.** Дослідити зв'язок між експресією рецепторів естрогену та прогестерону в пухлині в поєднанні з рівнями метаболічних гормонів у сироватці крові та прогресуванням пухлини у пацієнток із раком ендометрія. **Методи.** У дослідження було включено 100 пацієнток із раком ендометрія та 50 здорових жінок контрольної групи відповідного віку. Рівні естрадіолу, прогестерону, інсуліну, лептину та адипонектину в сироватці крові аналізували за допомогою хемілюмінесцентного імуноаналізу. Зразки пухлинної тканини забарвлювали з використанням моноклональних антитіл до ER та PR стандартним стрептавідин-біотиновим методом. Ядерне забарвлення ≥10% вважали позитивним. **Результати.** Показано, що більшість пухлин були ER-позитивними (68%) та PR-позитивними (54%), тоді як 27% були подвійно-негативними. Рівні естрадіолу, лептину та інсуліну в сироватці крові були значно вищими у пацієнток на пізніх стадіях, тоді як рівні прогестерону та адипонектину були значно нижчими порівняно з пацієнтками на ранніх стадіях. Результати кореляційного та регресійного аналізів показали, що незалежними предикторами прогресування пухлини були відсутність експресії ER та PR, високий рівень естрадіолу, високий рівень лептину та низький рівень адипонектину. **Висновки.** Втрата експресії ER/PR та метаболічний гормональний дисбаланс, що характеризується підвищенням рівня естрадіолу та лептину і зниженням рівня адипонектину, тісно пов'язані з прогресуванням раку ендометрія. Ці зміни можуть сприяти проліферативним сигнальним шляхам та запальним процесам, що призводить до підвищення агресивності пухлини та прогресування захворювання.

Ключові слова: рак ендометрія, рецептор естрогену, рецептор прогестерону, моноклональні антитіла, лептин, адипонектин, інсулін.

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