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Evaluation of Estrogen Receptor Alpha (ERα), Neuropilin-1 (NRP1), and E-Cadherin Expression in Normal, Hyperplastic, and Neoplastic Endometrium

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Abstract

Objectives: To evaluate the expression patterns of estrogen receptor alpha (ERα), neuropilin-1 (NRP1), and E-cadherin in normal, hyperplastic, and neoplastic endometrial tissues and to investigate their potential roles in endometrial carcinogenesis.

Materials and Methods: This retrospective observational immunohistochemical study was conducted at a tertiary care center between February 2021 and August 2022. Ninety-seven paraffin-embedded endometrial tissue specimens, including proliferative endometrium (n=23), endometrial hyperplasia without atypia (n=16), endometrial hyperplasia with atypia (n=13), Grade 1 endometrioid endometrial carcinoma (n=20), Grade 2 endometrioid endometrial carcinoma (n=14), and Grade 3 endometrioid endometrial carcinoma (n=11), were evaluated immunohistochemically for ERα, NRP1, and E-cadherin expression.

Results: ERα expression was significantly higher in endometrial hyperplasia without atypia compared with Grade 2/3 endometrioid endometrial carcinoma ($P<0.05$). NRP1 expression was lower in atypical hyperplasia than in proliferative endometrium ($P<0.05$), whereas significantly stronger NRP1 staining was observed in Grade 1 and Grade 2/3 endometrioid endometrial carcinoma compared with proliferative endometrium and hyperplastic lesions ($P<0.05$ for all comparisons). E-cadherin expression was significantly decreased in Grade 2/3 endometrioid endometrial carcinoma compared with proliferative endometrium, atypical hyperplasia, and Grade 1 carcinoma ($P<0.05$ for all comparisons).

Conclusions: Increased NRP1 expression together with reduced ERα and E-cadherin expression in higher-grade endometrial carcinomas suggests that these markers may be associated with endometrial carcinogenesis and tumor progression. Further studies are needed to clarify the underlying molecular mechanisms.

Keywords: Endometrial hyperplasia, Endometrial neoplasms, Estrogen receptor alpha, Neuropilin-1, E-cadherin

Introduction

Endometrial cancer ranks seventh among the most common types of cancer in the world and first among gynecologic cancers in developed countries (1). Endometrial hyperplasia is the hyperplastic changes occurring in the endometrial gland and stroma under the continuous effect of estrogen, unopposed by progesterone (2). Endometrial hyperplasia is clinically significant because it may present with or precede endometrial cancer (3). While the rate of transformation to cancer is 1-3% in hyperplasia without atypia, this rate increases to 8-29% in the presence of atypia (2).

Estrogen is considered a key modulator in the development, growth, invasion, and metastasis of tumors originating from the female genital tract and breast tissue (4). ERα is a critical mediator of hormonal response in estrogen-sensitive tissues such as the endometrium, breast, and bone (5). It is thought to play a pivotal role in developing endometrioid endometrial carcinoma, the most common histological subtype of endometrial neoplasms (6). Endometrial cancer is generally regarded as an estrogen-dependent malignancy in terms of tumor growth and progression. However, as endometrial cancer progresses, estrogen receptor expression diminishes, and the tumor eventually loses its dependence on estrogen for continued growth (7).

Cadherins are calcium-dependent transmembrane cell adhesion molecules. Different cadherins expressed on various cell types regulate epithelial, endothelial, and neural cell adhesion. E-cadherin, a receptor belonging to the cadherin superfamily, is an epithelial cell adhesion molecule that mediates cell–cell interactions through homophilic binding and is expressed in all proliferating epithelial cells derived from the ectoderm and endoderm (8). E-cadherin expression is critically important for regulating tumor cell apoptosis (9). Several studies have demonstrated reduced or aberrant expression of E-cadherin in various types of cancer (10). Disruptions

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Key Messages

- NRP1 expression increases significantly during progression from endometrial hyperplasia to endometrial carcinoma.
- Reduced ERα and E-cadherin expression is associated with higher-grade endometrial carcinoma.
- Combined evaluation of ERα, NRP1, and E-cadherin may improve understanding of endometrial carcinogenesis.

in the E-cadherin/catenin adhesion complex have been identified in gynecologic malignancies, including cervical, ovarian, and endometrial carcinomas (11).

Neuropilin-1 (NRP1) is a transmembrane glycoprotein that functions as a co-receptor for various structurally diverse ligands, including vascular endothelial growth factor (VEGF) (12). Research on NRP1 has spanned many fields, including the nervous system, angiogenesis, tumorigenesis, hematopoietic diseases, and the immune system (13). NRP1 is expressed in nearly all tumors, enabling it to play roles within tumor cells and the tumor microenvironment. Overexpression of NRP1 and elevated serum levels have been reported to promote tumor formation and metastasis in various cancers, particularly solid tumors (14). In patients with endometrial cancer, NRP1 expression is higher compared to healthy individuals and increases in parallel with advancing tumor grade (15).

It has been shown that 17-beta estradiol (17-β E_2) upregulates NRP1 expression in endometrial cells in a dose-dependent manner, and that high NRP1 expression leads to E-cadherin downregulation (16). Based on this information, and considering the role of stimulation by unopposed estrogen in the development of endometrial cancer, it was hypothesized that during the pathophysiological progression from normal endometrium to malignant endometrium, 17-β E_2 may increase NRP1 expression, thereby leading to E-cadherin downregulation.

This study aims to elucidate the molecular changes involved in developing endometrial cancer and contribute to advancing molecular approaches for early diagnosis and treatment. In this context, the study was designed to evaluate the expression levels of ERα, NRP1, and E-cadherin in benign proliferative phase endometrium, in endometrial hyperplasia without and with atypia, representing intermediate stages between normal endometrium and cancer, and in endometrial adenocarcinoma.

Materials and Methods

Clinical Data Collection and Tissue Handling

This retrospective observational immunohistochemical study was conducted at Kırıkkale University Hospital between February 2021 and August 2022 following Institutional Review Board approval (November 26, 2020; approval no. 2020.11.24). Pathological specimens from 97 patients who underwent hysterectomy or endometrial biopsy for abnormal uterine bleeding between 2011 and 2020 were included.

Cases were classified as proliferative endometrium, endometrial hyperplasia without atypia, endometrial hyperplasia with atypia, or endometrioid endometrial carcinoma according to pathology records. Patients with non-endometrioid endometrial cancers, concurrent pathological conditions (e.g., adenomyosis, endometriosis, cervical squamous cell carcinoma), chronic inflammation, or incomplete medical records were excluded. To minimize selection bias, all consecutive archived cases meeting the predefined inclusion and exclusion criteria during the study period were included in the analysis. Age, surgical history, and tumor grade data were obtained from archived records.

The sample size was determined by the availability of eligible archived paraffin-embedded endometrial tissue specimens during the study period. No a priori sample size or power calculation was performed because of the retrospective design. Nevertheless, the number of included cases was comparable to previous immunohistochemical studies evaluating similar biomarkers in endometrial cancer (15,17). This similarity should not be interpreted as a formal statistical justification for the sample size.

Histopathological Evaluation

Hematoxylin and eosin-stained slides were retrieved from the pathology archives and re-evaluated by the study pathologist. Diagnoses and classifications of endometrial hyperplasia and endometrioid endometrial carcinoma were established according to current WHO criteria (18).

The study included 23 proliferative endometrium cases, 29 endometrial hyperplasia cases (16 without atypia and 13 with atypia), and 45 endometrioid endometrial carcinoma cases (20 Grade 1, 14 Grade 2, and 11 Grade 3). Proliferative endometrium was selected as the normal control because it represents the physiological estrogen-responsive state of the endometrium and provides the most appropriate reference for evaluating the progression from normal endometrium to endometrial hyperplasia and endometrioid endometrial carcinoma.

Immunolocalization of ERα, NRP1, and E-Cadherin

Four-micron-thick sections obtained from archival paraffin blocks were mounted on poly-L-lysine-coated positively charged slides. The sections were deparaffinized at 65 °C for 1 hour and immunostained using an automated Ventana BenchMark XT system (Ventana Medical Systems, Basel, Switzerland). Antigen retrieval was performed using the Cell Conditioning 1 (CC1) protocol according to the manufacturer's recommendations. Primary antibodies included ERα (rabbit monoclonal, DAKO, Cat. No. IS08430-2, 1:100), NRP1 (mouse monoclonal, Santa Cruz Biotechnology, Cat. No. sc-5307, 1:100), and E-cadherin (rabbit monoclonal, Bio SB, Cat. No. BSB5464, 1:100). Antibody incubation was performed using the automated

staining protocol of the Ventana BenchMark XT system. Negative controls were prepared by omitting the primary antibody, whereas normal kidney tissue, uterine cervix, and colon adenocarcinoma served as positive controls for NRP1, ERα, and E-cadherin, respectively.

Evaluation of the Slides

Slides were evaluated using a dual-headed Leica DM LS2 light microscope (Solms, Germany). All immunohistochemical slides were evaluated by an experienced pathologist who was blinded to the clinical diagnosis and study group allocation. Nuclear staining was assessed for ERα, cytoplasmic staining for NRP1, and membranous staining for E-cadherin. For ERα and NRP1, both staining percentage and intensity were evaluated, whereas only staining intensity was assessed for E-cadherin.

The percentage of positive cells was categorized as 0, I (1–25%), II (26–50%), III (51–75%), and IV (76–100%). Staining intensity was classified as negative (–), weak (+), moderate (++), or strong (+++). Immunoreactive scores for ERα and NRP1 were calculated by multiplying staining percentage and intensity and categorized as negative (0–1), weak (2–3), moderate (4–8), or strong (9–12) (19).

Grade 2 and Grade 3 endometrioid endometrial carcinoma were analyzed as a combined group because of the relatively small number of cases in each subgroup, in order to improve the statistical robustness of the analyses.

Statistical Analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Data were expressed as number (%) or mean ± standard deviation. Normality was assessed using the Shapiro-Wilk test. Continuous variables were compared using the Kruskal-Wallis and Mann-Whitney U tests, while categorical variables were analyzed using the chi-square or Fisher's exact test. A P value <0.05 was considered statistically significant. No formal adjustment for multiple pairwise comparisons was performed because this was an exploratory retrospective immunohistochemical study. Therefore, the results of pairwise comparisons should be interpreted with appropriate caution.

Results

The mean age of the patients included in the study was 46 ± 7.3 (32-58), 47 ± 8.0 (33-67), 53 ± 8.7 (32-69), 58 ± 7.5 (46-69), 64 ± 8.6 (54-82), and 60 ± 12.0 (37-76) years in the proliferative endometrium, endometrial hyperplasia without atypia, endometrial hyperplasia with atypia, Grade 1, Grade 2, and Grade 3 endometrioid endometrial carcinoma groups, respectively. According to age, there was a statistically significant difference between the proliferative endometrium group and the groups with endometrial hyperplasia without atypia, Grade 1, Grade 2, and Grade 3 endometrioid endometrial carcinoma, as well as between the proliferative endometrium group and the endometrial hyperplasia with atypia group (P<0.01). No statistically significant difference was observed among the Grade 1, Grade 2, and Grade 3 endometrioid endometrial carcinoma groups ($P \geq 0.05$).

As evaluated by immunoreactive score, all specimens of endometrial hyperplasia without atypia showed more intense ERα staining in epithelial nuclei than Grade 2/3 endometrioid endometrial carcinoma ($P < 0.05$). No other statistically significant differences were observed between the groups. The details are given in Table 1. Representative photomicrographs in Figure 1 demonstrate the differences in ERα nuclear immunoreactivity among proliferative endometrium, endometrial hyperplasia, and endometrioid endometrial carcinoma, supporting the quantitative findings.

In all specimens, proliferative endometrium showed stronger cytoplasmic NRP1 staining than endometrial hyperplasia with atypia, as evaluated by immunoreactive score ($P < 0.05$). Stronger cytoplasmic NRP1 staining was also observed in both Grade 1 and Grade 2/3 endometrioid endometrial carcinoma compared with proliferative endometrium ($P < 0.001$) and endometrial hyperplasia with and without atypia ($P < 0.001$ and $P < 0.05$, respectively). The details are given in Table 2. Representative photomicrographs in Figure 2 illustrate

Table 1. Estrogen Receptor Alpha Expression in Epithelial Nucleus Evaluated by the Immunoreactive Score (Staining Intensity x Percentage of Positive Cells)

Type of tissue	Number of cases	Immunoreactive score for ERα			
		Negative	Mild	Moderate	Strongly positive
Proliferative endometrium	23	0 (0)	1 (4.4)	3 (13)	19 (82.6)
Endometrial hyperplasia without atypia	16	0 (0)	0 (0)	0 (0)[a]	16 (100)[a]
Endometrial hyperplasia with atypia	13	1 (7.7)	0 (0)	2 (15.4)	10 (76.9)
Grade 1 endometrioid endometrial carcinoma	20	0 (0)	0 (0)	5 (25)	15 (75)
Grade 2/3 endometrioid endometrial carcinoma	25	0 (0)	2 (8)	8 (32)	15 (60)

ERα, Estrogen receptor alpha.
Results are expressed as the number (percentage)
The histoscore values from 0 to 12 were grouped to indicate negative (0-1), mild (2–3), moderate (4-8), and strongly positive (9–12) expression
[a] Significance when compared with the group of high grade endometrioid endometrial carcinoma, $P < 0.05$

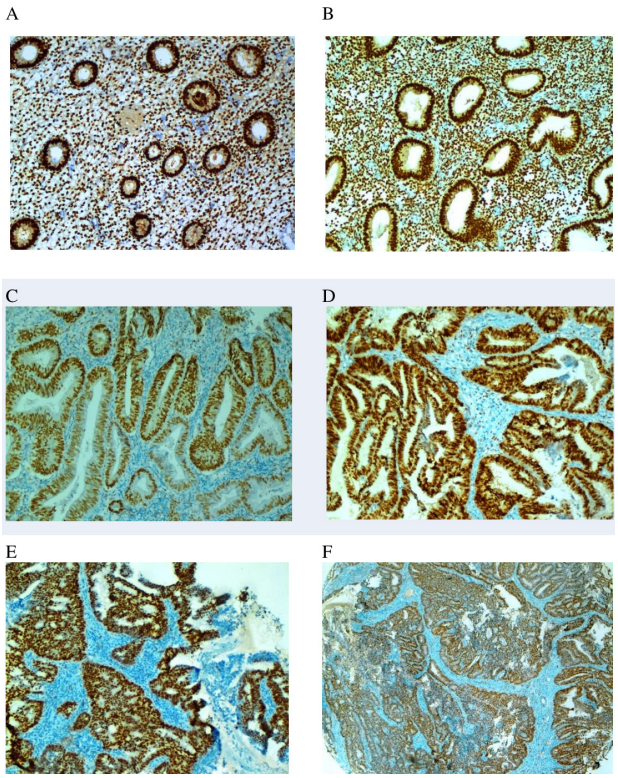

Figure 1. Immunohistochemical Staining Examples With Estrogen Receptor Alpha (ERα). (A) In normal proliferative endometrium, strong (+++) staining in 76–100% (IV) of the cells. (B) In endometrial hyperplasia without atypia, strong (+++) staining in 76–100% (IV) of the cells. (C) In atypical endometrial hyperplasia, strong (+++) staining in 76–100% (IV) of the cells. (D) In Grade 1 endometrioid endometrial carcinoma, strong (+++) staining in 76–100% (IV) of the cells. (E) In Grade 2 endometrioid endometrial carcinoma, strong (+++) staining in 76–100% (IV) of the cells. (F) In Grade 3 endometrioid endometrial carcinoma, moderate (++) staining in 51–75% (III) of the cells. [Original magnifications: 100× (A); 100× (B); 100× (C); 100× (D); 100× (E); 40× (F)].

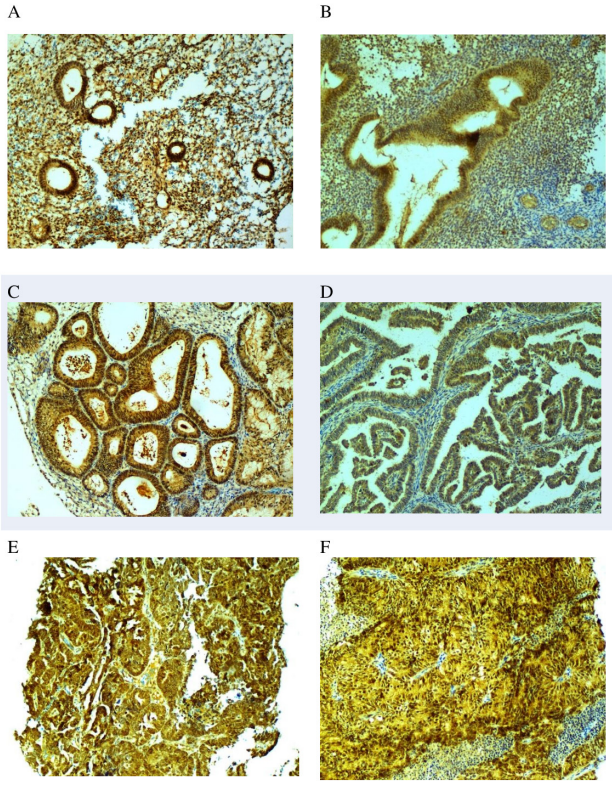

Figure 2. Immunohistochemical staining examples with Neuropilin-1 (NRP1). (A) In normal proliferative endometrium, strong (+++) staining in 76–100% (IV) of the cells. (B) In endometrial hyperplasia without atypia, strong (+++) staining in 76–100% (IV) of the cells. (C) In atypical endometrial hyperplasia, strong (+++) staining in 76–100% (IV) of the cells. (D) In Grade 1 endometrioid endometrial carcinoma, strong (+++) staining in 76–100% (IV) of the cells. (E) In Grade 2 endometrioid endometrial carcinoma, strong (+++) staining in 76–100% (IV) of the cells. (F) In Grade 3 endometrioid endometrial carcinoma, strong (+++) staining in 76–100% (Score IV) of the cells. [Original magnifications: 100× (A); 100× (B); 100× (C); 100× (D); 100× (E); 100× (F)].

the progressive increase in NRP1 immunoreactivity from benign to malignant endometrial tissues, consistent with the quantitative immunohistochemical analysis.

As detailed in Table 3, epithelial membranous E-cadherin staining was stronger in proliferative endometrium, endometrial hyperplasia with atypia, and Grade 1 endometrioid endometrial carcinoma than in Grade 2/3 endometrioid endometrial carcinoma ($P<0.05$, $P<0.05$, and $P<0.01$, respectively). Representative photomicrographs in Figure 3 demonstrate the reduced membranous E-cadherin expression in Grade 2/3 endometrioid endometrial carcinoma, supporting the quantitative findings.

Table 2. Neuropilin 1 Expression in Epithelial Cytoplasm Evaluated by the Immunoreactive Score (Staining Intensity x Percentage of Positive Cells)

Type of tissue	Number of cases	Immunoreactive score for NRP1			
		Negative	Mild	Moderate	Strongly positive
Proliferative endometrium	23	0 (0)	0 (0)	23 (100)[a,b,c]	0b,c
Endometrial hyperplasia without atypia	16	0 (0)	1 (6.3)	13 (81.2) [b,c]	2 (12.5) [b,c]
Endometrial hyperplasia with atypia	13	2 (15.4)	0 (0)	10 (76.9) [b,c]	1 (7.7) [b,c]
Grade 1 endometrioid endometrial carcinoma	20	2 (10)	0 (0)	2 (10)	16 (80)
Grade 2/3 endometrioid endometrial carcinoma	25	2 (8)	1 (4)	9 (36)	13 (52)

NRP1, Neuropilin 1.
The histoscore values from 0 to 12 were grouped to indicate negative (0-1), mild (2–3), moderate (4-8), and strongly positive (9–12) expression
[a] Significance when compared with the group of endometrial hyperplasia with atypia, $P < 0.05$.
[b] Significance when compared with the group of Grade 1 endometrioid endometrial carcinoma, $P < 0.001$.
[c] Significance when compared with the group of Grade 2/3 endometrioid endometrial carcinoma, $P < 0.05$.

Table 3. E-Cadherin Expression in Epithelial Membrane Evaluated by Staining Intensity

	Proliferative endometrium (N=23)	Endometrial hyperplasia (N=29)		Endometrioid endometrial carcinoma (N=45)	
		Without atypia (n=16)	With atypia (n=13)	Grade 1 (n=20)	Grade 2/3 (n=25)
-	0	0	0	0	1 (4)
+	0	0	0	0	2 (8)
++	1 (4.3)	1 (6.3)	0	0	5 (20)
+++	22 (95.7)	15 (93.7)	13 (100)	20 (100)	17 (68)[a,b,c]

Results are expressed as the number (percentage).
Negative staining (-); weak staining (+); moderate staining (++), intense staining (+++).
[a] Significance when compared to the group of proliferative endometrium.
[b] Significance when compared to the group of atypical endometrial hyperplasia.
[c] Significance when compared to the group of Grade 1 endometrioid endometrial carcinoma.

Discussion

Considering the role of unopposed estrogen stimulation in the development of endometrial cancer, it has been proposed that 17-β estradiol (17-β E_2) may lead to E-cadherin downregulation by increasing NRP1 expression during the pathophysiological process from normal endometrium to malignant endometrium, and our study was conducted in line with this hypothesis.

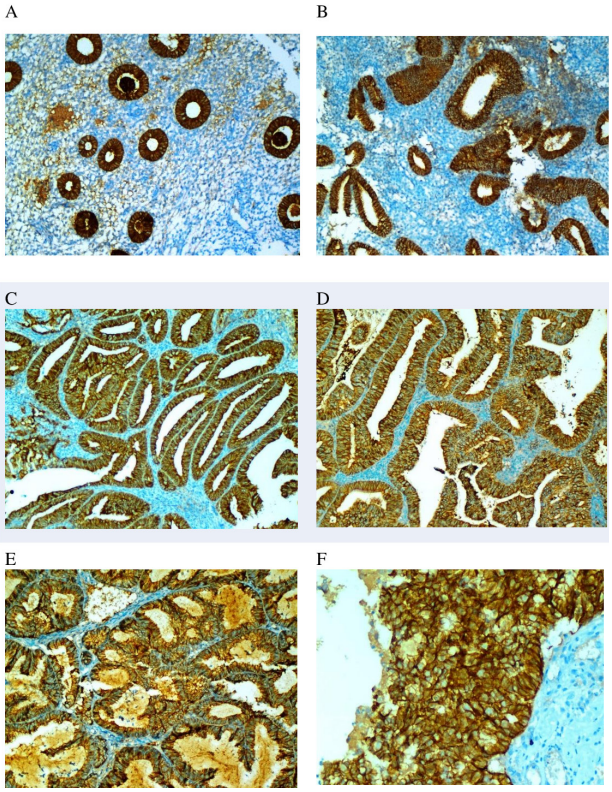

Figure 3. Immunohistochemical staining examples with E-cadherin. (A) In normal proliferative endometrium, strong (+++) staining in 76–100% (IV) of the cells. (B) In endometrial hyperplasia without atypia, strong (+++) staining in 76–100% (IV) of the cells. (C) In atypical endometrial hyperplasia, strong (+++) staining in 76–100% (IV) of the cells. (D) In Grade 1 endometrioid endometrial carcinoma, strong (+++) staining in 76–100% (IV) of the cells. (E) In Grade 2 endometrioid endometrial carcinoma, strong (+++) staining in 76–100% (IV) of the cells. (F) In Grade 3 endometrioid endometrial carcinoma, strong (+++) staining in 76–100% (IV) of the cells. [Original magnifications: 100× (A); 100× (B); 100× (C); 100× (D); 100× (E); 100× (F)]

In our study, strong ERα expression in epithelial nuclei gradually decreased from proliferative endometrium and endometrial hyperplasia without atypia (82.6% and 100%, respectively) to endometrial hyperplasia with atypia (76.9%), Grade 1 endometrioid endometrial carcinoma (75%), and Grade 2/3 endometrioid endometrial carcinoma (60%). A significant decrease was observed in the Grade 2/3 endometrioid endometrial carcinoma group compared with the endometrial hyperplasia without atypia group. Similar findings have been reported previously. Hu et al evaluated ERα expression immunohistochemically in 114 patients with endometrial hyperplasia and endometrioid endometrial carcinoma and demonstrated that ERα expression increased from normal proliferative endometrium to endometrial hyperplasia without atypia but decreased in atypical endometrial hyperplasia and endometrioid endometrial carcinoma (20). Likewise, Fujimoto and Sato reported significantly higher ERα mRNA expression in normal endometrium than in endometrioid endometrial carcinoma, with a progressive decrease from Grade 1 to Grade 3 tumors. They also demonstrated that reduced ERα mRNA expression was associated with advanced tumor stage and deeper myometrial invasion, suggesting a role in tumor progression (7). Similarly, Fujimoto et al reported that reduced ERα expression was associated with poor prognosis and metastasis in endometrial cancer (4). Jongen et al evaluated the prognostic value of ERα by immunohistochemistry in 315 patients with endometrioid endometrial carcinoma. ERα expression was detected in 58.7% of tumors and was significantly associated with early-stage and low-grade disease. Moreover, reduced ERα expression was associated with higher mortality, whereas patients with ERα-positive tumors had better overall survival (21). Similarly, Zannoni et al evaluated ERα expression immunohistochemically in 121 patients with endometrioid endometrial carcinoma and reported that ERα/ERβ1 and ERα/ERβ2 ratios below 1 were associated with an increased risk of mortality. These findings suggest that these ratios may serve as prognostic markers in endometrioid endometrial carcinoma (22).

In the study by Mylonas et al, the ERα/ERβ ratio

was statistically significantly decreased in malignant endometrial tissue compared to normal endometrium (23). Overall, our findings regarding ERα are consistent with previous studies. ERα expression gradually decreases from proliferative endometrium and endometrial hyperplasia without atypia to endometrial hyperplasia with atypia and grades 1 and 2/3 endometrioid endometrial carcinoma. However, this decrease is statistically significant only in moderately and poorly differentiated endometrioid endometrial carcinoma compared to endometrial hyperplasia without atypia. Although nearly all type I endometrial tumors express estrogen receptors (ERs), higher ER expression is associated with better outcomes, as it indicates a well-differentiated tumor that remains under the influence of 17-β estradiol (17-β E_2) (24).

In our study, cells from the proliferative endometrium group showed the highest rate (100%) of NRP1 expression with moderate positivity. Although this expression was significantly higher compared to endometrial hyperplasia with atypia (76.9%), both Grade 1 and Grade 2/3 endometrioid endometrial carcinoma expressed NRP1 with strong positivity (80% and 52%, respectively), more than proliferative endometrium and endometrial hyperplasia without and with atypia (12.5% and 7.7%, respectively). In the study by Okon et al, the relationship between NRP1 and tumor-developing cytokines in endometrial cancer specimens was investigated. The study found that NRP1 expression was correlated with elevated serum levels of specific cytokines and a metastatic protein. Eighty-three endometrial cancer cases were examined, and 87% of these specimens exhibited moderate to strong NRP1 expression. Additionally, since most of the examined cases consisted of early-stage cancer cases, NRP1 may be an indicator in the early stages of endometrial cancer development (25). The results of our study support the findings of this previous study, suggesting that a gradual increment in NRP1 expression may be involved in the malignant transformation of pre-malignant endometrium.

In our study, Grade 2/3 endometrioid endometrial carcinoma expressed E-cadherin with significantly less intensity (68%) compared to proliferative endometrium (95.7%), endometrial hyperplasia with atypia (100%), and Grade 1 endometrioid endometrial carcinoma (100%). The study by Moreno-Bueno et al was conducted on 21 endometrial hyperplasias with atypia, 95 endometrioid endometrial carcinomas, and 33 non-endometrioid endometrial carcinomas. A decrease in E-cadherin level was observed in 57.8% of the patients. The number of cases with decreased E-cadherin level was found to be significantly higher in non-endometrioid endometrial carcinomas and in advanced-stage (stage 3–4) cancer cases ($P < 0.05$). Additionally, in endometrioid endometrial carcinoma cases, the number of cases with decreased E-cadherin level was found to increase significantly as the tumor stage advanced (43.5% in stage 1, 62.5% in stage 2, and 87.5% in stage 3–4) ($P < 0.05$) (8). In the meta-analysis conducted by Zheng et al, endometrial cancer patients with decreased E-cadherin levels were found to have a worse prognosis compared to those with normal or high E-cadherin levels (26). In the study by Schlosshauer et al, E-cadherin expression was evaluated immunohistochemically in serous and endometrioid endometrial carcinoma samples. Among 17 Grade 3 endometrioid endometrial carcinoma cases, moderate to strong E-cadherin expression was observed in only 1 case (6%) (27). As our findings support, we may suggest that the E-cadherin level is decreased in endometrial cancer, and with increasing tumor grade.

Considering our findings, which are consistent with previous reports, altered expression patterns of ERα, NRP1, and E-cadherin appear to be associated with the progression from proliferative endometrium to endometrioid endometrial carcinoma. Previous experimental studies have suggested that estrogen signaling may increase NRP1 expression and may be associated with reduced E-cadherin expression (16). However, because the present study was a retrospective observational immunohistochemical study, our findings should be interpreted as associations rather than evidence of a causal or mechanistic relationship. Further functional studies are needed to clarify the molecular interactions among these biomarkers during endometrial carcinogenesis.

Limitations of the Study

Our study has several limitations. First, this was a single-center retrospective observational immunohistochemical study with a relatively limited sample size, and no a priori sample size or power calculation was performed. Second, the study groups differed significantly in age. Since age and menopausal status are closely associated with endometrial carcinogenesis and hormone receptor expression, age may have acted as a confounding factor and may have partially influenced the observed immunohistochemical findings. Furthermore, only univariate statistical analyses were performed, and multivariable analyses adjusting for potential confounding factors could not be conducted. In addition, no formal correction for multiple pairwise comparisons was applied, which may have increased the risk of type I error. Formal assessment of interobserver or intraobserver reproducibility was also not performed. Other limitations include the absence of serum and tissue estradiol, E-cadherin, and NRP1 measurements, the lack of clinicopathological prognostic data (e.g., FIGO stage, myometrial invasion, lymphovascular space invasion, recurrence, and survival), and the absence of treatment and follow-up data for non-malignant cases.

Conclusions

In conclusion, increased NRP1 expression accompanied by lower ERα and E-cadherin expression in higher-grade

endometrioid endometrial carcinoma may be associated with the progression from proliferative and hyperplastic endometrium to malignant endometrial lesions. However, because this was a retrospective observational immunohistochemical study, these findings should be interpreted as associations rather than evidence of a causal or mechanistic relationship. Further functional and prospective studies are needed to clarify the molecular interactions among ERα, NRP1, and E-cadherin in endometrial carcinogenesis.

Authors' Contribution

Conceptualization: Ebu Bekir Sıddık Yılmaz, Mertihan Kurdoğlu.
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Methodology: Ebu Bekir Sıddık Yılmaz, Mertihan Kurdoğlu, Tuba Devrim.
Project administration: Mertihan Kurdoğlu.
Resources: Mertihan Kurdoğlu, Tuba Devrim.
Supervision: Mertihan Kurdoğlu.
Validation: Mertihan Kurdoğlu, Tuba Devrim.
Visualization: Ebu Bekir Sıddık Yılmaz, Tuba Devrim.
Writing–original draft: Ebu Bekir Sıddık Yılmaz.
Writing–review & editing: Mertihan Kurdoğlu, Tuba Devrim, Şükrü Bakırcı, Cemile Dayangan Sayan, Zehra Sema Özkan, Nevin Sağsöz.

Conflict of Interests

Authors declare that they have no conflict of interests.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

The authors declare that no generative AI or AI-assisted technologies were used in the writing or preparation of this manuscript.

Ethical Issues

The study protocol was approved by the Kırıkkale University Ethics Committee (Approval No. 2020.11.24; November 26, 2020).

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