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ESTROGEN RECEPTOR AND BCL-2 EXPRESSION IN POSTMENOPAUSAL ENDOMETRIAL POLYPS: INSIGHTS INTO HORMONAL AND APOPTOTIC PATHWAYS

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ABSTRACT

Background: Endometrial polyps (EPs) represent one of the most frequent uterine abnormalities observed in postmenopausal women, and they are often linked to episodes of irregular or abnormal uterine bleeding. and, occasionally, premalignant or malignant transformation. Hormonal imbalance and apoptotic dysregulation have been implicated, but the molecular mechanisms underlying polyp persistence remain unclear, particularly the interplay between estrogen receptor (ER) signaling and the anti-apoptotic marker Bcl-2. **Objective:** To evaluate ER expression in postmenopausal EPs, explore its association with Bcl-2, and assess correlations with age and specimen type. **Methods:** A retrospective–prospective case series was conducted on 50 postmenopausal women (aged 50–75 years) with histologically confirmed EPs collected from Al-Khansaa Teaching Hospital and private laboratories in Mosul, Iraq (October 2021–October 2022). Paraffin-embedded blocks were stained with Hematoxylin–Eosin and immunohistochemistry for ER and Bcl-2. Staining intensity was semi-quantitatively scored in glandular epithelial nuclei. Data were analyzed using Chi-square, Fisher's exact test, Spearman correlation, and logistic regression (SPSS v.25). **Results:** ER expression was detected in 37 of 50 cases (74%), most frequently at score 3+ (42%), whereas 26% were negative. Bcl-2 positivity was observed in 49 cases (98%), including 92% of ER-negative polyps. No significant association was found between ER and Bcl-2 expression ($p = 0.20$; Spearman $r = 0.21$). Logistic regression showed no significant effect of age or specimen type on ER status ($p > 0.05$). **Conclusion:** Postmenopausal EPs demonstrate frequent ER positivity and diffuse Bcl-2 expression, suggesting combined mechanisms of estrogen sensitivity and apoptotic resistance. The absence of significant ER–Bcl-2 correlation indicates multifactorial pathways in polyp pathogenesis. Immunohistochemical profiling of ER and Bcl-2 may assist in risk stratification, particularly in women receiving tamoxifen therapy.

KEYWORDS: Endometrial polyp; Estrogen receptor; Bcl-2; Postmenopausal women; Tamoxifen; Immunohistochemistry.

INTRODUCTION

Endometrial polyps (EPs) are focal overgrowths of non-malignant endometrial glands and stromal tissue, characterized by their irregular architecture and extension into the uterine cavity.[1,2] They represent one of the most common uterine pathologies, with prevalence rates reported between **20% and 30%** in postmenopausal women.[3,4] While often asymptomatic, EPs are strongly associated with **abnormal uterine bleeding (AUB)**, infertility, and in rare cases, premalignant or malignant lesions.[5,6] Their clinical importance is further emphasized in women Women undergoing hormone replacement therapy (HRT) or receiving tamoxifen as part of breast cancer management, in whom polyps are detected with higher frequency.[4,7,8]

The etiopathogenesis of EPs is **multifactorial** and remains incompletely understood. It has been suggested that **hormonal imbalance** plays a central role: endometrial polyps exhibit both estrogen and progesterone receptors, with studies reporting **increased ER and reduced PR expression** compared to adjacent endometrium, leading to sustained proliferation and impaired shedding.[9,10,11] In addition, resistance to apoptosis appears critical, as reflected by the strong expression of the **anti-apoptotic protein Bcl-2**, which prolongs cellular survival within the glands and

stroma.[12,13] Other molecular alterations, including **Ki-67 overexpression, KRAS mutations, aromatase-mediated local hyperestrogenism, and c-erbB2 amplification**, have been implicated in polyp growth and their rare progression to malignancy.[14,15]

Despite these insights, a key knowledge gap persists regarding the **interaction between ER signaling and apoptotic regulators such as Bcl-2 in postmenopausal endometrial polyps**. Previous studies have shown inconsistent results: while some authors reported a positive correlation between ER and Bcl-2 expression.[16] others found no significant association, suggesting that apoptosis dysregulation may proceed independently of estrogen pathways.[36,38] Moreover, most available data derive from small, heterogeneous cohorts, with limited studies addressing Middle Eastern populations, where variations in lifestyle, obesity, and metabolic risk factors may further modulate polyp biology.[17,18]

This study was conducted to assess the expression of estrogen receptors (ER) within the glandular epithelium of endometrial polyps among postmenopausal women, to assess its association with Bcl-2 expression, and to analyze its correlation with patients' age and specimen type. By addressing this gap, the study seeks to clarify the molecular mechanisms underpinning polyp development in postmenopause and to provide insights relevant to early detection and risk stratification.

MATERIALS AND METHODS

Sample Selection

All cases including in the study represented consecutive samples of histologically confirmed postmenopausal endometrial polyps, collected between October 2021 and October 2022. No selective inclusion or exclusion was applied beyond the diagnostic confirmation, to minimize sampling bias.

Ethical Approval

The research was carried out in accordance with established ethical standards governing medical studies that utilize human tissue samples. Approval for the study protocol was granted by the Institutional Review Board (IRB) at Al-Khansa Teaching Hospital in Mosul, Iraq. under approval number.

IRB/AKTH/2022/041. Additional specimens were processed from some private laboratories in Mosul city, Iraq, and immunohistochemical staining procedures were carried out in a certified private laboratory.

Study Design and Setting

This study employed a combined retrospective and prospective case series design conducted between October 2021 and October 2022. A total of 50 formalin-fixed, paraffin-embedded (FFPE) tissue blocks were analyzed, obtained either from total abdominal hysterectomy (TAH) or dilation and curettage (D&C) specimens of postmenopausal women diagnosed with endometrial polyps. All specimens were collected from Al-Khansaa Teaching Hospital and several private pathology laboratories in Mosul, Iraq. Immunohistochemical procedures were carried out in a private laboratory, while histopathological evaluation and interpretation were performed at the Pathology Department, College of Medicine, University of Mosul.

Specimen Processing and Histopathology

- For D&C samples, the entire specimen was embedded for histopathological examination.
- For hysterectomy specimens, representative sections were prepared using a rotary microtome and processed for Hematoxylin and Eosin (H&E) staining.
- Histological diagnosis of endometrial polyp (EP) was confirmed based on the presence of **cystically dilated glands, fibrotic stroma, and thick-walled blood vessels**.

Hematoxylin and Eosin Staining

1. Deparaffinization: Three changes of xylene, 10 minutes each.
2. Rehydration: Two changes of graded alcohols (absolute to 70%), 1–2 minutes each.
3. Nuclear staining: Harris hematoxylin for 5–15 minutes.
4. Differentiation: 1% acid alcohol, followed by washing.
5. Bluing: Running tap water for 10 minutes.
6. Counterstaining: 2–3 minutes in eosin.
7. Dehydration, clearing, and mounting with DPX.

Immunohistochemistry (IHC) Procedure Automated immunohistochemical staining was carried out using the Dako Autostainer Link48 system following heat-induced epitope retrieval in the PT Link/Dako unit (97 °C for 20 minutes in citrate buffer, pH 6.0). To inhibit endogenous peroxidase activity, sections were treated with 3% hydrogen peroxide for 10 minutes, and non-specific antibody binding was reduced by applying Ultra V Block. The slides were then incubated overnight at 4 °C with primary monoclonal antibodies as specified.

Estrogen Receptor (ER): clone SP1, a rabbit monoclonal antibody (dilution 1:100; Cell Marque, Rocklin, CA, USA; catalog number 200R-18). **Bcl-2:** clone 124, a mouse-derived monoclonal antibody applied at a 1:100 dilution (Dako/Agilent, Santa Clara, CA, USA; Cat. No. M0887. Immunoreactivity was visualized using a conventional avidin–biotin–peroxidase complex kit (ABC kit; Vector Laboratories, Burlingame, CA, USA; catalog no. PK-6100), with diaminobenzidine (DAB) employed as the chromogenic substrate. The sections were subsequently counterstained with hematoxylin and mounted in DPX medium.

Controls

- Positive controls: breast carcinoma (ER) and follicular lymphoma (Bcl-2).

- Negative controls: omission of the primary antibody, replaced with non-immune serum.

Evaluation of Immunostaining and Inter-observer Variability

Immunostaining was evaluated in glandular epithelial nuclei only. A case was defined as positive if ≥1% of nuclei demonstrated distinct brown chromogenic staining. The semi-quantitative scoring system was applied as follows.

0 = no staining;
1+ = 1–25%;
2+ = 26–50%;
3+ = 51–75%;
4+ = >75%.

Two independent pathologists (with >10 years' experience each) performed blinded slide evaluations. Inter-observer agreement was assessed using Cohen's kappa (κ) statistic; a κ ≥0.75 was considered excellent agreement. Discrepant cases were reviewed jointly to reach consensus.

Statistical Analysis

Statistical analyses were carried out using SPSS software, version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive outcomes were presented as frequencies and percentages. The associations between estrogen receptor (ER) expression, age categories, and specimen type were examined using the Chi-square test or Fisher's exact test when applicable. To explore the relationship between ER and Bcl-2 expression, Spearman's rank correlation was applied. In order to account for possible confounding factors such as age, body mass index (BMI), and specimen type, binary logistic regression analysis was performed. A p-value of less than 0.05 was regarded as statistically significant, and 95% confidence intervals were provided. Additionally, statistical power analysis was conducted to verify the adequacy of the sample size.

RESULTS

Clinicopathological Characteristics

A total of **50 postmenopausal women** with histologically confirmed endometrial polyps were included in this study. The patients' ages ranged between 50 and 75 years, with a mean of **58.9 ± 7.1 years**. The highest frequency of cases was observed in the **50–54 year group (32%)**, followed by 60–64 years (22%).

Regarding specimen type, **31 cases (62.0%)** were obtained through dilation and curettage (D&C), while **19 cases (38.0%)** were derived from total abdominal hysterectomy (TAH).

Table 1: ER expression scores according to different age groups.

Age group (years)	ER Negative n (%)	ER +1 n (%)	ER +2 n (%)	ER +3 n (%)	P-value
50–54	5 (38.5%)	1 (20.0%)	2 (18.2%)	8 (38.1%)	0.09
55–59	4 (30.8%)	3 (60.0%)	4 (36.4%)	0 (0.0%)	
60–64	1 (7.7%)	1 (20.0%)	1 (9.1%)	8 (38.1%)	
65–69	2 (15.4%)	0 (0.0%)	3 (27.3%)	2 (9.5%)	
71+	1 (7.7%)	0 (0.0%)	1 (9.1%)	3 (14.3%)	

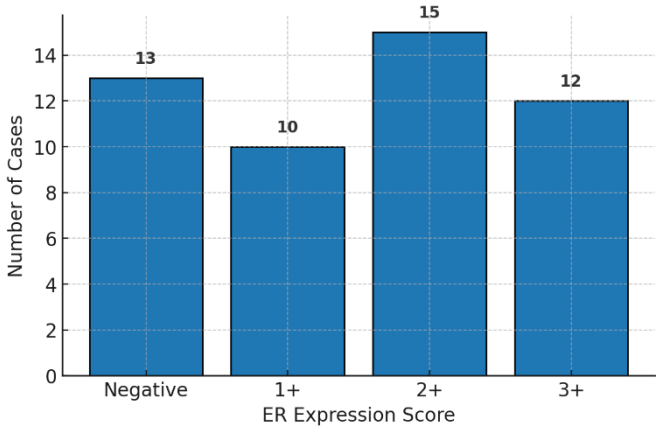

Figure 1: Distribution of estrogen receptor (ER) expression scores (Negative, 1+, 2+, 3+) among the study cases. No statistically important difference was discovered (Chi-square test, p > 0.05).

Estrogen Receptor (ER) Expression

Table 2 illustrates the association between estrogen receptor (ER) and Bcl-2 expression in postmenopausal endometrial polyps. Among the 50 cases analyzed, ER positivity was detected in 37 cases (74.0%), all of which also demonstrated Bcl-2 expression. Conversely, of the 13 ER-negative cases (26.0%), 12 (92.3%) remained positive for Bcl-2, and only a single case (2.0%) was negative for both markers. This pattern indicates that while ER expression is common in endometrial polyps,

Bcl-2 positivity is nearly universal, occurring independently of ER status.

Statistical analysis revealed no marked association among ER and Bcl-2 expression (Chi-square test, p = 0.20), and the weak positive correlation observed (Spearman r = 0.21, p = 0.15) did not reach statistical significance. These findings suggest that resistance to apoptosis, mediated by Bcl-2, may persist regardless of ER signaling, highlighting the multifactorial molecular pathways underpinning polyp persistence. Clinically, the observation that ER-negative polyps still exhibit strong Bcl-2 expression emphasizes that estrogen-independent mechanisms of survival and growth may contribute to their pathogenesis, which could be particularly relevant in the context of malignant transformation risk. Representative photomicrographs showing absence of ER immunostaining reactivity in endometrial glandular cells (score 0) are presented in Figure 2.

Representative photomicrographs illustrate these findings: Figure 2 depicts the absence of ER immunostaining in glandular epithelial nuclei (score 0), corresponding to ER-negative cases identified in the table. In contrast, Figure 3 presents the spectrum of ER staining intensities, ranging from weak nuclear reactivity (1+) to moderate (2+) and strong diffuse expression (3+). Together, these images provide visual confirmation of the semi-quantitative scoring system used to classify ER immunoreactivity across the study cohort.

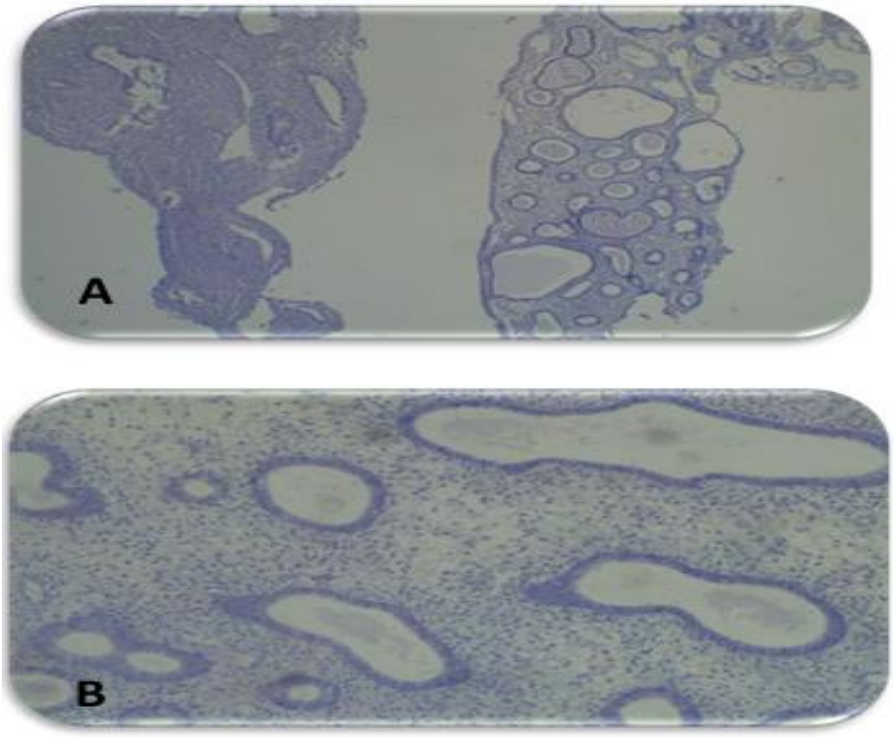

Figure 2: Representative photomicrographs showing absence of ER immunostaining reactivity in endometrial glandular cells, graded as score 0 (A, 40X; B, 100X).

For clearer visualization, the distribution of ER and Bcl-2 expression among the study cohort was also illustrated using bar charts (Figure X), highlighting the predominance of Bcl-2 positivity regardless of ER status.

Table 2: Association between Estrogen Receptor (ER) and Bcl-2 expression in endometrial polyps occurring in postmenopausal women.

ER status	Total n (%)	Bcl-2 Negative n (%)	Bcl-2 Positive n (%)	Chi-square (p)	Spearman r (p)
ER Negative	13 (26.0%)	1 (2.0%)	12 (24.0%)		
ER Positive	37 (74.0%)	0 (0.0%)	37 (74.0%)		
Total	50 (100.0%)	1 (2.0%)	49 (98.0%)	0.20	0.21 (0.15)

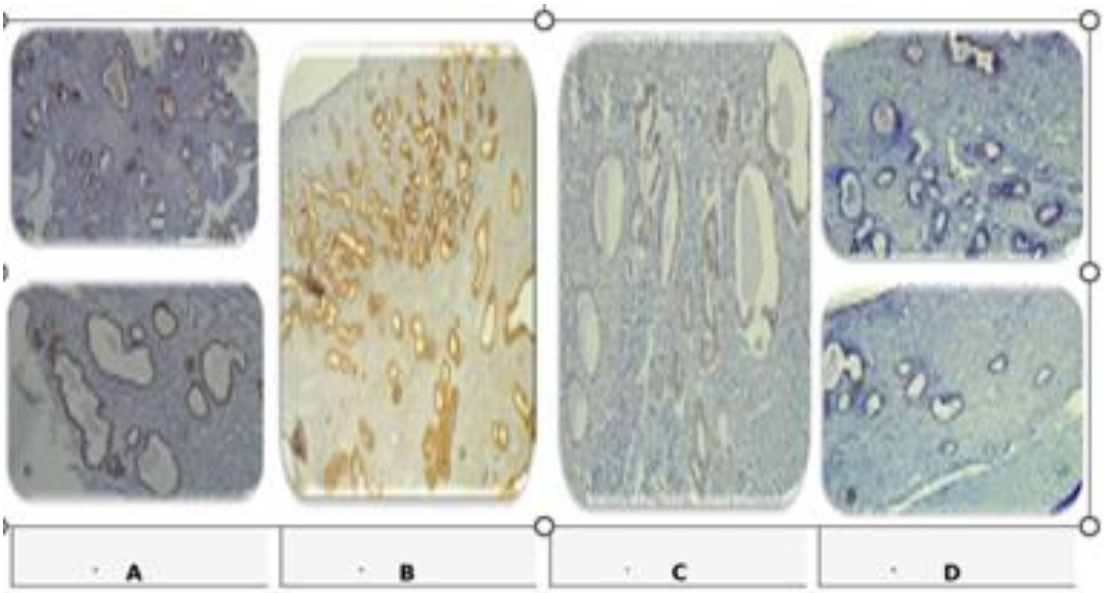

Figure 3: Representative photomicrographs of ER immunostaining showing different intensity scores: (A) Negative, (B) Weak (1+), (C) Moderate (2+), and (D) Strong (3+).

DISCUSSION

Endometrial polyps (EPs) are benign endometrial proliferations frequently observed among postmenopausal women, where they are commonly correlated with abnormal uterine bleeding and less frequently, with premalignant or malignant transformation.[19,20] The pathogenesis of EPs remains incompletely understood; however, accumulating evidence suggests that deregulated hormonal signaling, altered apoptotic control, and molecular aberrations contribute to their development and persistence.[21] In this study, the expression of estrogen receptors (ER) was identified in 74% of cases, with the predominant pattern being strong positivity (score 3+). This finding is in accordance with Voutsadakis.[22], who reported higher ER expression in postmenopausal polyps compared with atrophic endometrium, indicating that estrogen signaling continues to play a role in the pathogenesis of EPs despite the low systemic estrogen levels characteristic of menopause. Similarly, Yang et al.[23] in North America demonstrated enhanced sensitivity of polyp glands to steroid hormones, suggesting that localized ER overexpression may compensate for diminished circulating estrogens. Lathigara et al.[24], also documented significantly higher ER expression in polyp glandular epithelium compared with adjacent endometrium, further supporting the hypothesis that endometrial polyps represent a hyper-responsive microenvironment. On the molecular level, ER-α and ER-β function as transcription factors regulating target gene expression in a ligand-dependent manner.[25] In EPs, ER-α predominance facilitates uncontrolled mucosal proliferation, while the reduced counter-regulatory role of progesterone receptors (PRs), as noted in prior studies[26], diminishes cyclic endometrial control. This imbalance renders polyps relatively insensitive to progesterone-induced decidualization, thereby preventing their regular shedding (8,9In endometrial polyps, the pathogenic role of impaired apoptosis becomes evident through the upregulation of anti-apoptotic proteins, most notably Bcl-2. In this study, Bcl-2 expression was positive in nearly all cases (98%), with no statistically significant correlation between ER and Bcl-2 expression ($p = 0.20$). These findings align with Mahadik et al.[27], who observed strong Bcl-2 expression in both hyperplastic and atrophic polyps, suggesting that resistance to apoptosis prolongs cellular survival regardless of proliferative activity. While Kawiak and Kostecka.[28] demonstrated a positive correlation between ER and Bcl-2 expression, our data suggest that alternative apoptotic pathways—independent of ER stimulation—may sustain Bcl-2 upregulation. Moreover, this discrepancy may reflect variations in population genetics, sample size, and methodological approaches. Beyond ER/Bcl-2, additional molecular pathways have been implicated in EP pathogenesis. For instance, increased expression of Ki-67, a proliferation marker, distinguishes premenopausal from postmenopausal EPs, indicating enhanced stromal cell division in hormonally active environments.[29] Similarly, KRAS mutations have been documented in EPs, with reports showing that up to 57% of cases harbor clonal cytogenetic rearrangements, particularly at chromosome 12q13, which are associated with endometrial hyperplasia and carcinogenesis.[30] Furthermore, overexpression of aromatase (CYP19A1) within stromal cells contributes to localized estrogen production, creating a paracrine hyperestrogenic milieu that may promote polyp growth and recurrence after conservative treatment.[31] The overexpression of c-erbB2 (HER2/neu) has also been associated with enhanced proliferative capacity of endometrial glands in postmenopausal EPs, highlighting its potential role in malignant transformation.[32] Clinically, the observation that 26% of cases were ER-negative yet Bcl-2 positive suggests heterogeneity in EP biology. As proposed by Vieira et al.[33], reduced ER expression in premalignant

or malignant polyps may serve as a risk factor for neoplastic transformation, where growth is sustained by ER-independent oncogenic mechanisms. Similarly, Banibakhsh[34], demonstrated that tamoxifen exposure significantly decreases ER expression but increases Bcl-2, reflecting its mixed agonist-antagonist properties on the endometrium. These findings highlight the complexity of hormonal modulation, particularly in women undergoing adjuvant tamoxifen therapy for breast cancer. Taken together, our findings underscore that postmenopausal endometrial polyps are characterized by predominant ER overexpression and diffuse Bcl-2 positivity, indicating dual mechanisms of sustained proliferation and apoptosis resistance. Nonetheless, the lack of correlation between ER and Bcl-2 in this cohort suggests that apoptotic dysregulation may persist independently of estrogen receptor signaling. This molecular interplay emphasizes the need for further research incorporating additional markers (e.g., Ki-67, p53, survivin) and genomic profiling to clarify the pathways driving polyp development and malignant potential.

The outcomes of this investigation underscore how dysregulated estrogen receptor signaling, coupled with apoptosis suppression through Bcl-2 expression, may represent key mechanisms in the formation and persistence of endometrial polyps in postmenopausal women. While ER overexpression remains the dominant feature, the absence of a strong correlation with Bcl-2 implies multifactorial control mechanisms. Integrating immunohistochemical profiling with molecular genetics may improve risk stratification and inform the clinical management of postmenopausal endometrial polyps.

The failure to demonstrate a significant association between ER and Bcl-2 expression ($p > 0.05$) might be influenced by the study's limited sample size, which could have reduced the statistical power to detect subtle relationships as well as the absence of additional molecular markers such as Ki-67 or p53, which could provide further insight into proliferative and apoptotic pathways. Clinically, the persistence of Bcl-2 positivity in ER-negative polyps underscores the possibility of estrogen-independent survival mechanisms, which may have implications for the risk stratification of patients and the consideration of preventive or therapeutic interventions in postmenopausal women with recurrent polyps.

CONCLUSION

Endometrial polyps in postmenopausal women showed a predominance of strong ER expression and diffuse Bcl-2 positivity, indicating that both enhanced estrogen sensitivity and apoptotic resistance contribute to their persistence. The lack of a considerable correlation between ER and Bcl-2 suggests multiple molecular pathways are involved, including local hyperestrogenism and apoptotic dysregulation. Clinically, these findings support the value of immunohistochemical evaluation of ER and Bcl-2 in postmenopausal polyps, especially in women on tamoxifen therapy, to better assess malignant potential.

Limitations

This study is confined by the relatively small sample size and the reliance on a single-center design, which could limit the broader applicability of the results. Another limitation is the exclusive reliance on immunohistochemistry, without incorporating additional molecular markers such as Ki-67, p53, or genomic profiling (KRAS, HER2), which could provide complementary insights. Moreover, clinical and hormonal data such as body mass index, tamoxifen exposure, and hormone replacement therapy were not available, restricting the ability to correlate molecular findings with clinical risk factors.

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Conflicted interest: None.

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