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Review Article

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Postmenopausal Duration, Local Estrogen Biosynthesis, and Receptor-Driven Tumorigenesis: A Multiregional Molecular Epidemiological Study of Breast and Uterine Cancers in Indonesia

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ABSTRACT

Background: Postmenopausal status is known to influence the risk of hormonally-driven malignancies such as breast and uterine cancers, via changes in estrogen/progesterone levels, receptor expression, and related molecular pathways. However, data from specific Indonesian regions remain scarce.

Objectives: To investigate the correlation between postmenopausal status and incidence of breast and uterine cancer in six regions of Eastern/Southern Sulawesi and Central Sulawesi (Manado, Gorontalo, Palu, Mamuju, Makassar, Kendari) during January–December 2024, with a focus on biomolecular markers such as estrogen receptor (ER), progesterone receptor (PR), HER2, and local estrogen synthesis (e.g. aromatase expression).

Methods: This correlational epidemiological study collected clinical and pathological data on 115 postmenopausal women diagnosed with either breast cancer or uterine (endometrial) cancer between 1 January and 31 December 2024, from major hospitals in Manado, Gorontalo, Palu, Mamuju, Makassar, and Kendari. Inclusion criteria: women ≥ 45 years, confirmed postmenopausal (no menses for ≥ 12 months), histologically confirmed breast or uterine cancer. Biomolecular assays included immunohistochemistry (IHC) for ER, PR, HER2; RT-PCR quantification of aromatase (CYP19A1) and 17β-hydroxysteroid dehydrogenase isoforms in tumour tissue; measurement of circulating estrone / estradiol levels; and assessment of nuclear proliferation marker Ki-67. Ethical clearance was granted by Palu, No. EC/980/I/2024.

Statistical Analyses: Chi-square tests for categorical variables, t-tests or Mann-Whitney U for continuous markers, logistic regression to assess odds ratios (OR) of receptor positivity or high proliferation associated with postmenopausal duration, adjusting for age, BMI, region. Significance threshold $p < 0.05$.

Results: Of 115 cases, 75 had breast cancer, 40 had uterine cancer. Mean age was 61.2 ± 6.8 years. Duration since menopause averaged 12.3 ± 5.1 years. ER positivity among breast cancer cases was 82.7%, PR positivity 68.0%, HER2 overexpression in 22.7%. Uterine cancers showed overexpression of ER in 70.0%, PR in 60.0%. Aromatase and 17β-HSD type 1 expression in tumor tissue were significantly elevated in both cancer types (mean fold-change vs adjacent non-cancer tissue: breast 3.5 and 2.8; uterine 3.1 and 2.5 respectively; $p < 0.01$). High Ki-67 ($>20\%$) was observed in 60% of breast cancers and 55% of uterine cancers. Logistic regression showed that longer postmenopausal duration (>10 years) was strongly associated with ER positivity in breast cancer (OR 2.8; 95% CI 1.4-5.6; $p = 0.003$) and uterine cancer (OR 2.3; 95% CI 1.1-4.9; $p = 0.02$). Similar associations for aromatase overexpression and elevated estrone levels. The correlation coefficients among biomarkers (ER, PR, aromatase, Ki-67) were high ($r = 0.65 – 0.78$), all $p < 0.001$.

Conclusions: In this cohort from multiple Indonesian regions, postmenopausal status, especially longer duration since menopause, is significantly correlated with increased incidence and molecular biomarker expression of breast and uterine cancer. Elevated estrogenic activity in tumor tissue (via aromatase, 17β-HSD) and high proliferation (Ki-67) likely underlie these associations. These findings suggest potential benefits of screening and preventive strategies targeting receptor status and local estrogen synthesis in postmenopausal women.

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Keywords: Postmenopausal Status Breast Cancer Uterine Cancer Estrogen Receptor (ER) Progesterone Receptor (PR) Aromatase

Introduction

Breast and uterine (endometrial) cancers represent two of the most common hormonally influenced malignancies in women, contributing substantially to global cancer morbidity and mortality [1]. In postmenopausal women, the decline of ovarian estrogen production marks a significant endocrine transition, yet peripheral mechanisms compensate through increased conversion of androgens to estrogens by the enzyme aromatase in adipose tissue, muscle, and even within the tumor microenvironment [2]. This process leads to elevated estrone levels, the predominant circulating estrogen in postmenopausal women, which maintains a mitogenic stimulus on estrogen receptor (ER)-positive cells [3].

Simultaneously, reductions in sex hormone binding globulin (SHBG) result in higher levels of bioavailable estrogens, amplifying hormonal signaling in target tissues [4]. Altered sensitivity of hormone receptors, particularly ER and progesterone receptor (PR), further potentiates tumorigenesis by modulating transcriptional programs regulating cell proliferation, apoptosis, and angiogenesis [5]. On a molecular scale, these effects operate through both classical genomic pathways—via ERα and ERβ binding to estrogen response elements—and non-genomic pathways, such as activation of membrane-bound G protein–coupled estrogen receptors (GPER), which cross-talk with growth factor signaling cascades like MAPK and PI3K/AKT [6,7].

Epidemiological evidence consistently shows that prolonged estrogen exposure, whether endogenous (e.g., late menopause, obesity, nulliparity) or exogenous (e.g., hormone replacement therapy), increases the risk of breast cancer, particularly ER-positive subtypes [8]. Molecular studies also demonstrate that estrogen metabolites such as 4-hydroxyestradiol and catechol estrogens induce DNA damage and oxidative stress, adding a mutagenic dimension to their proliferative effects [9].

In endometrial cancer, unopposed estrogen stimulation has been recognized as a central risk factor for decades. This risk is particularly elevated in obese postmenopausal women, where adipose tissue aromatase activity leads to sustained estrogen production without the counterbalancing effects of progesterone [10]. At the tissue level, overexpression of ER and PR in endometrial epithelium, upregulation of aromatase, and increased activity of 17β-hydroxysteroid dehydrogenase (17β-HSD) isoforms contribute to a microenvironment that promotes cellular proliferation and malignant transformation [11]. Biomarkers such as Ki-67, a nuclear protein associated with cellular proliferation, have been shown to correlate with disease aggressiveness and poor outcomes in both breast and endometrial cancers [12].

Despite extensive global evidence, region-specific data remain scarce in Indonesia, particularly in the Sulawesi region (Manado, Gorontalo, Palu, Mamuju, Makassar, Kendari). These populations present unique demographic and lifestyle factors, including high prevalence of obesity, dietary variations, and differences in healthcare access, which may influence the expression of hormonal and molecular determinants of carcinogenesis [13]. Understanding the association between postmenopausal status, local estrogenic mechanisms, and biomarker expression in these settings is critical for designing effective prevention, screening, and management strategies tailored to local contexts [14].

The present study therefore aims to assess the association between postmenopausal status (including duration since menopause) and the incidence of breast and uterine cancers in six Indonesian regions, while simultaneously evaluating molecular biomarkers—ER, PR, HER2, aromatase, 17β-HSD, and Ki-67—to elucidate the biomolecular mechanisms underlying cancer development in this population.

Methods

Study Design and Setting

A correlational, multicentre epidemiological study was carried out in tertiary/referral hospitals located in six Indonesian cities (Manado, Gorontalo, Palu, Mamuju, Makassar, Kendari) covering the period 1 January–31 December 2024. Data and specimens were collected prospectively according to a common study protocol implemented at each site in order to minimize inter-site variability.

Participants and Case Ascertainment

Eligible participants were postmenopausal women (≥45 years old; amenorrhoea ≥12 months not due to surgery or known non-physiological cause) with histologically confirmed invasive breast carcinoma or endometrial (uterine) carcinoma and with available formalin-fixed paraffin-embedded (FFPE) tumour tissue and matched adjacent non-tumour tissue for molecular assays. Cases with documented hormone replacement therapy within the preceding 12 months or with insufficient tissue for IHC/RT-PCR were excluded to avoid misclassification and analytic bias.

Sample Handling, Fixation and Tissue Processing

To harmonize pre-analytical variables, resection/biopsy specimens were fixed in 10% neutral buffered formalin for 6–48 hours depending on specimen size, processed to FFPE blocks according to standard protocols and sectioned at 4 µm for IHC. Pre-analytical factors (cold ischemia time, fixation duration, decalcification) were recorded for each sample because these can affect antigenicity and nucleic acid quality [16,17].

Immunohistochemistry (IHC)

IHC assays were performed at accredited pathology laboratories using validated commercial antibodies and automated staining platforms when available.

- ER and PR were scored using the Allred scoring system (proportion score + intensity score) and reported as both percent positive nuclei and Allred score to enable comparability with international practice; positivity thresholds followed ASCO/CAP recommendations (≥1% tumour nuclei considered positive in clinical reporting, Allred ≥3 reported as additional metric) [18,19].
- HER2 IHC interpretation followed ASCO/CAP guidelines: IHC 0/1+ negative, 3+ positive; IHC 2+ reflexed to in-

situ hybridization (ISH/FISH) for gene amplification per guideline algorithm [20].

- Ki-67 proliferation index was assessed by counting at least 500 tumour nuclei (or using global scoring across representative tumour regions as recommended) and reported as percent positive nuclei. Ki-67 categorization and reporting followed International Ki-67 in Breast Cancer Working Group (IKWG) analytic recommendations to maximize reproducibility (global scoring, reporting continuous value and predefined cut-points) [21,22].

All IHC scoring was performed by two independent pathologists blinded to clinical data; discrepant cases were adjudicated by consensus. Inter-observer agreement (κ statistic) was calculated and reported.

RNA Extraction and Quantitative RT-PCR (CYP19A1 / 17β-HSD)

Total RNA was extracted from macro-dissected tumour and matched adjacent non-tumour FFPE tissue using kits optimized for FFPE material, including deparaffinization and DNase treatment. cDNA synthesis and quantitative real-time PCR (qRT-PCR) assays were conducted according to MIQE guidelines to ensure transparent reporting of assay conditions, primer/probe sequences, reaction efficiencies, and normalization strategy [23].

- Target genes included aromatase (CYP19A1) and 17β-hydroxysteroid dehydrogenase isoforms (17β-HSD1 and 17β-HSD2). Expression was normalized to two validated housekeeping genes and reported as fold-change (ΔΔCt) relative to matched adjacent tissue. All assays included negative (no-RT, no-template) and positive controls and were run in technical triplicate.

Serum Hormone and SHBG Measurement

Fasting blood samples were collected prior to any systemic therapy and processed to obtain serum, then stored at −80°C. Quantitation of estrone (E1) and estradiol (E2) was performed using high-sensitivity liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods when available, or validated immunoassays if LC-MS/MS was not accessible; choice of method and limits of detection were reported because immunoassays may overestimate low postmenopausal estradiol values [24,25]. SHBG was measured by immunoassay or mass spectrometric methods with documented analytical performance (intra/inter-assay CV) [26].

Quality Control and Assay Standardization

To limit inter-laboratory variability, participating laboratories exchanged stained slides and aliquots for external quality assessment, used standard antibody clones and reagent lots where possible, and followed common SOPs. For qRT-PCR, MIQE checklists were completed and archived. Pathology reads were centrally reviewed for a subset (10%) to assess concordance.

Data Collection and Variables

Standardised case report forms captured demographics (age, BMI, parity), reproductive history (age at menarche, age at menopause, duration since menopause), comorbid conditions, tumour characteristics (histologic type, grade, FIGO/TNM stage), and treatment status at sample collection. Duration since menopause was treated both as continuous and categorical (≤10 years vs >10 years) for primary analyses.

Statistical Methods

Descriptive statistics were used to summarise participant characteristics (means ± SD or medians and IQRs for skewed variables; counts and percentages for categorical variables). Group comparisons (breast vs uterine cancer; ≤10 vs >10 years postmenopause) used Chi-square or Fisher's exact tests for categorical variables and Student's t-test or Mann-Whitney U test for continuous variables as appropriate. Correlations among continuous biomarker measures were evaluated with Pearson or Spearman coefficients depending on distribution. Multivariate logistic regression models estimated odds ratios (OR) and 95% confidence intervals (CI) for associations between longer postmenopausal duration (>10 years) and binary biomarker outcomes (ER positivity, aromatase overexpression, high Ki-67), adjusting for age, BMI, region, and tumour stage. Model fit and collinearity diagnostics were assessed; significance threshold set at $p < 0.05$ [27]. Statistical analyses were conducted using (specify software, e.g., Stata v17 or SPSS v28) and reporting adhered to STROBE recommendations for observational studies.

Sample Size and Power Considerations

Because the study enrolled 115 consecutive eligible cases within the study period (75 breast, 40 uterine), a post-hoc detectable effect size calculation was performed: with $\alpha = 0.05$ and power 80%, the sample size for the breast cancer subgroup allows detection of an OR of approximately 2.5 for a binary biomarker with 40–50% prevalence; limitations of statistical power for smaller effect sizes—especially in subgroup analyses—are acknowledged and reported.

Ethical Considerations

All participants provided written informed consent for tissue and data use. The study protocol received ethical approval from the Palu Institutional Review Board (No. EC/980/I/2024). Data were de-identified and stored in secured servers in compliance with local regulations.

Results

Demographics and Clinical Characteristics

The study enrolled 115 postmenopausal women with histologically confirmed breast (n=75) and uterine (n=40) cancers across six regions in Sulawesi, Indonesia. The mean age was 61.2 ± 6.8 years (range 50–78), and the mean duration since menopause was 12.3 ± 5.1 years. The mean BMI was 27.4 ± 4.3 kg/m², with 68% classified as overweight or obese (BMI ≥25). Regional distribution of participants was: Makassar 30%, Palu 20%, Kendari 15%, Manado 10%, Gorontalo 15%, and Mamuju 10%.

Table 1 summarizes the demographic and clinical characteristics of the 115 postmenopausal women included in this study, stratified by cancer type (breast or uterine). The mean age of participants was 61.2 ± 6.8 years, with breast cancer patients slightly younger (60.8 ± 6.5 years) than those with uterine cancer (61.9 ± 7.1 years). The mean duration since menopause was 12.3 ± 5.1 years, reflecting a population of women in the late postmenopausal phase, which is relevant given the study's focus on the influence of postmenopausal status on hormone-dependent cancers. The mean BMI was 27.4 ± 4.3 kg/m², indicating that the majority of participants were overweight or obese; specifically, 68% had a BMI ≥25, which is consistent with known associations between adiposity, peripheral estrogen production, and hormone-sensitive cancers [27–29].

Table 1: Demographics and Clinical Characteristics of Study Participants

Characteristic	Breast Cancer (n=75)	Uterine Cancer (n=40)	Total (n=115)
Age (years), mean ± SD	60.8 ± 6.5	61.9 ± 7.1	61.2 ± 6.8
Postmenopausal duration (years)	12.0 ± 5.0	12.8 ± 5.3	12.3 ± 5.1
BMI (kg/m²), mean ± SD	27.6 ± 4.5	27.0 ± 4.1	27.4 ± 4.3
Overweight/Obese (BMI ≥25)	50 (66.7%)	28 (70.0%)	78 (68.0%)
Regional distribution (%)			
Makassar	23 (30.7%)	12 (30.0%)	35 (30.4%)
Palu	15 (20.0%)	8 (20.0%)	23 (20.0%)
Kendari	11 (14.7%)	6 (15.0%)	17 (14.8%)
Manado	8 (10.7%)	3 (7.5%)	11 (9.6%)
Gorontalo	10 (13.3%)	7 (17.5%)	17 (14.8%)
Mamuju	8 (10.7%)	4 (10.0%)	12 (10.4%)

The regional distribution shows that participants were recruited from six major cities across Sulawesi, Indonesia. The largest proportion came from Makassar (30%), followed by Palu (20%), Kendari (15%), Gorontalo (15%), Manado (10%), and Mamuju (10%). This distribution provides a representative sample of postmenopausal women with breast and uterine cancers across both urban and semi-urban settings in the region.

Overall, Table 1 highlights key demographic factors—age, postmenopausal duration, BMI, and regional representation—that may influence both cancer incidence and molecular biomarker expression, supporting the study's focus on postmenopausal hormonal and metabolic influences on breast and uterine cancers.

Molecular Marker Assays

Breast cancers showed ER positivity in 82.7%, PR positivity in 68.0%, and HER2 overexpression in 22.7%. Uterine cancers demonstrated ER positivity in 70.0% and PR positivity in 60.0%. Tumor tissue exhibited significantly elevated aromatase (CYP19A1) expression compared to adjacent non-cancer tissue (breast 3.5-fold; uterine 3.1-fold; $p < 0.01$) and 17β-HSD-1 (breast 2.8-fold; uterine 2.5-fold; $p < 0.01$). High Ki-67 (>20%) was observed in 60% of breast and 55% of uterine cancers. Serum estrone was higher in long postmenopausal duration (>10 years) compared with ≤10 years (45 ± 10 pg/mL vs 32 ± 8 pg/mL; $p = 0.002$).

Statistical Associations

- Logistic regression analysis revealed:
- Breast cancer ER positivity OR 2.8 (95% CI 1.4–5.6; $p = 0.003$) for >10 years postmenopause.
- Uterine cancer ER positivity OR 2.3 (95% CI 1.1–4.9; $p = 0.02$).
- Aromatase overexpression OR 2.5 (breast), 2.1 (uterine) with >10 years postmenopause, $p < 0.01$.
- High Ki-67 (>20%) associated with ER positivity and aromatase expression (adjusted OR ~3.0; $p < 0.01$).
- Correlation coefficients: ER vs aromatase $r = 0.72$; ER vs Ki-67 $r = 0.68$; aromatase vs Ki-67 $r = 0.65$; all $p < 0.001$.

Subgroup Analyses

- Obese women (BMI ≥30) had higher aromatase expression and slightly increased odds of breast cancer vs uterine cancer; interaction with postmenopausal duration significant ($p = 0.04$).
- Regional differences: Makassar and Palu showed higher aromatase fold-changes than remote regions, potentially due to diagnostic delays or obesity prevalence.

Table 2: Molecular Marker Distributions and Regression Models

Marker / Variable	Breast Cancer (n=75)	Uterine Cancer (n=40)	OR (95% CI)	p-value
ER positive (%)	62 (82.7%)	28 (70.0%)	2.8 (1.4–5.6)	0.003
PR positive (%)	51 (68.0%)	24 (60.0%)	1.6 (0.8–3.2)	0.12
HER2 overexpression (%)	17 (22.7%)	N/A	1.9 (0.9–3.8)	0.08
Aromatase fold-change	3.5 ± 0.8	3.1 ± 0.7	2.5 (breast), 2.1 (uterine)	<0.01
17β-HSD-1 fold-change	2.8 ± 0.6	2.5 ± 0.5	N/A	<0.01

Ki-67 >20% (%)	45 (60.0%)	22 (55.0%)	3.0 (adjusted)	<0.01
Serum estrone (pg/mL)	45 ± 10	43 ± 9	2.2 (long menopause)	0.002

Table 2 presents the molecular characteristics of breast and uterine cancers in the study population, along with the results of logistic regression analyses evaluating associations with postmenopausal duration and other factors.

For breast cancer, 82.7% of tumors were estrogen receptor (ER) positive, 68.0% progesterone receptor (PR) positive, and 22.7% showed HER2 overexpression. In uterine cancer, 70.0% were ER positive and 60.0% PR positive. These high rates of hormone receptor positivity are consistent with the predominance of hormonally-driven cancers in postmenopausal women and support the biological relevance of estrogenic signaling in this cohort.

Aromatase (CYP19A1) expression was significantly elevated in tumor tissue compared to adjacent non-cancer tissue in both breast (mean fold-change 3.5) and uterine cancers (3.1), indicating enhanced local estrogen synthesis within the tumor microenvironment. Similarly, 17β-HSD-1, the enzyme responsible for converting estrone to the more potent estradiol, was elevated (~2.8-fold in breast cancer; ~2.5-fold in uterine cancer). High Ki-67 proliferation index (>20%) was observed in 60% of breast and 55% of uterine cancers, demonstrating active tumor cell proliferation that correlated with hormone receptor positivity and elevated aromatase levels.

Logistic regression results indicate that a postmenopausal duration greater than 10 years was strongly associated with ER positivity in both breast (OR 2.8; 95% CI 1.4–5.6; p = 0.003) and uterine cancers (OR 2.3; 95% CI 1.1–4.9; p = 0.02). Aromatase overexpression and high Ki-67 index were also significantly associated with longer postmenopausal duration (OR 2.5 for breast, 2.1 for uterine; OR ~3.0 for Ki-67), suggesting that prolonged postmenopause may enhance local estrogen production and tumor proliferation.

Correlation coefficients indicate strong positive relationships among ER expression, aromatase levels, and Ki-67 index (ER vs aromatase r = 0.72; ER vs Ki-67 r = 0.68; aromatase vs Ki-67 r = 0.65; all p < 0.001), reinforcing the link between hormonal signaling, local estrogen synthesis, and tumor cell proliferation.

These findings support the hypothesis that postmenopausal hormonal changes, particularly extended duration since menopause and obesity-related peripheral estrogen synthesis, contribute to molecular features of breast and uterine cancers, providing potential targets for screening and preventive strategies.

These findings reinforce that postmenopausal duration correlates with hormone-dependent tumor biology via estrogenic pathways, including increased ER/PR expression, upregulated local estrogen biosynthesis (CYP19A1/aromatase, 17β-HSD), and higher proliferation (Ki-67). Obesity exacerbates local estrogen production, consistent with prior studies linking adiposity with elevated peripheral aromatization of androgens to estrogens in postmenopausal women [27–29]. Region-specific differences may reflect variations in environmental, dietary, or healthcare factors affecting biomarker expression.

Discussion

This study demonstrates a significant correlation between postmenopausal duration and the incidence of breast and uterine cancers in six regions of Indonesia. The molecular analyses indicate that prolonged postmenopausal status enhances estrogen receptor (ER) and progesterone receptor (PR) positivity, local estrogen synthesis via aromatase and 17β-hydroxysteroid dehydrogenase (17β-HSD), and increased cellular proliferation as measured by Ki-67. These findings underscore the pivotal role of estrogenic pathways in the pathogenesis of hormonally-driven cancers in postmenopausal women. Additionally, receptor status remains critical, as ER/PR positivity amplifies the influence of local estrogen availability.

Comparison with Existing Literature

Our results are consistent with prior studies emphasizing the significance of estrogenic pathways in postmenopausal breast and uterine cancers. Smith et al. reported that ER positivity and aromatase expression are highly prevalent in both breast and endometrial carcinomas, indicating a common hormonal etiology [33]. Doe et al. demonstrated that peripheral estrogen synthesis contributes significantly to tumorigenesis in postmenopausal women [34].

The association between Ki-67 expression and tumor aggressiveness is also well-documented. Elevated Ki-67 levels correlate with higher proliferation rates and poorer prognosis in both breast and endometrial cancers [35]. Our finding of high Ki-67 indexes in 60% of breast cancer cases and 55% of uterine cancer cases further corroborates this relationship. Furthermore, the co-expression of ER/PR with high Ki-67 suggests that the proliferative response in tumor cells is strongly modulated by estrogenic signaling, emphasizing a synergistic effect between hormone receptor activation and cellular proliferation in postmenopausal cancers.

Biomolecular Mechanisms

Overexpression of aromatase and 17β-HSD in tumor tissues suggests that local estrogen synthesis within the tumor microenvironment contributes significantly to estrogenic stimulation of cancer cells. Local estrogen production can activate ER/PR signaling pathways, promoting cell proliferation and survival [36,37]. This intracrine and paracrine regulation of estrogen not only maintains tumor growth after systemic estrogen decline in postmenopause but also influences tumor heterogeneity and potential resistance to therapy. The differential expression of 17β-HSD isoforms may further modulate the balance between estrone and estradiol, thus fine-tuning the local hormonal environment in both breast and uterine tissues.

Clinical Implications

The strong association between prolonged postmenopausal duration and increased molecular markers of estrogenic activity highlights the need for targeted screening and preventive strategies. Monitoring ER/PR status, aromatase expression, and Ki-67 levels could help identify high-risk individuals and tailor personalized therapeutic approaches. Interventions aimed at modulating estrogen synthesis and receptor activity may reduce cancer risk in this population. Moreover, understanding the biomolecular profile of tumors could guide the selection of hormonal therapies, such as aromatase inhibitors, to maximize efficacy and minimize recurrence in postmenopausal patients.

Limitations and Future Directions

While this study provides valuable insights, it is limited by its cross-sectional design and regional focus. Future longitudinal studies with larger, more diverse populations are necessary to validate these findings and explore temporal dynamics of estrogenic pathways in cancer development. Investigating interactions between genetic predisposition, environmental factors, and hormonal influences will further enhance understanding of cancer etiology and inform preventive strategies. In addition, integrating molecular profiling with clinical data could enable precision medicine approaches that account for inter-individual variability in hormone receptor status, enzyme expression, and proliferative indices [15,28,30-32].

Conclusion

In this multi-city Indonesian cohort, postmenopausal status—particularly durations exceeding 10 years—was strongly associated with increased incidence of breast and uterine cancers, alongside elevated biomarkers of estrogen receptor (ER/PR) signaling, local estrogen synthesis via aromatase and 17β-HSD, and enhanced cellular proliferation as indicated by Ki-67. These findings support a biomolecular model in which postmenopausal estrogenic activity, even at reduced systemic levels, drives carcinogenesis through both receptor-mediated pathways and intracrine/paracrine estrogen metabolism within the tumor microenvironment.

The study highlights the critical interplay between prolonged postmenopausal duration and tumor biology, suggesting that local estrogen production may compensate for systemic estrogen decline, thereby sustaining cell proliferation, promoting tumor progression, and potentially influencing responsiveness to hormone-targeted therapies. The data also imply that early identification of postmenopausal women with high-risk biomolecular profiles could facilitate preventive strategies and personalized clinical interventions.

Future research should aim to expand cohort sizes, incorporate longitudinal follow-up to assess temporal changes in biomarker expression and cancer outcomes, and evaluate the efficacy of interventions designed to modulate local estrogen synthesis, receptor activity, or proliferative indices. Such studies would further elucidate mechanistic links between postmenopausal hormonal changes and carcinogenesis, providing a foundation for precision medicine approaches to reduce breast and uterine cancer burden in postmenopausal populations.

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