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Evaluation of hPG_{80} (Circulating Progastrin) as a Diagnostic Biomarker for Early Detection of Breast Cancer in Young Women in the United Arab Emirates

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Abstract

Background/Aim: Breast cancer (BC) is the most commonly diagnosed cancer worldwide, with rising incidence among women under 46 years - particularly in the United Arab Emirates (UAE). Despite this, no effective screening tools exist for this population. This study evaluated, for the first time, the diagnostic potential of hPG_{80} (circulating progastrin), a promising multi-cancer blood biomarker, in young women with BC through a monocentric prospective clinical trial at the University Hospital of Sharjah, UAE.

Patients and Methods: Plasma hPG_{80} levels were measured using the DxPG80.lab ELISA kit (Biodena Care, France) in blood samples. The study enrolled 50 treatment-naïve BC patients -21 under 46 years- along with 47 asymptomatic individuals under 45, and 78 asymptomatic individuals above 45. Diagnostic accuracy was assessed using receiver operating characteristic (ROC) curves and area under the curve (AUC) analyses.

Results: hPG_{80} levels were significantly higher in BC patients compared to asymptomatic individuals [median: 3.55 pM, interquartile range (IQR)=1.38-4.89 *vs.* 1.66 pM, IQR: 0.00-3.51; p=0.0006], with an AUC of 0.68 [95% confidence interval (CI)=0.58-0.77; p=0.0008]. Among young women, hPG_{80} was also elevated in BC patients (median: 2.24 pM, IQR=0.87-4.09) *versus* asymptomatic individuals (median: 1.66 pM, IQR=0.00-2.47; p=0.0425), with an AUC of 0.65 (95%CI=0.50-0.80; p=0.0443). Using the kit's limit of quantification (3.3 pM) as cutoff, sensitivity was 47.6%, specificity 89.4%, negative predictive value 79.2%, and positive predictive value 66.7% for distinguishing early-onset BC from asymptomatic individuals.

Conclusion: hPG_{80} may serve as a useful blood-based biomarker to support BC screening in young, high-risk women, particularly when combined with imaging. Validation in larger cohorts is warranted to confirm its role in early BC detection.

Keywords: hPG_{80}, breast cancer, young women, blood-based biomarker.

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Introduction

Breast cancer (BC) is the most diagnosed cancer type in the world. According to GLOBOCAN data, an estimated 2.3 million new cases and 670,000 deaths from BC occurred worldwide in 2022 (1). These figures represent 25.0% of all new cancer cases and 15.5% of cancer-related deaths among females. In the United States, only 4% of new breast cancer cases in 2019 occurred in women under 40 years old (2). In contrast, low- and middle-income countries (LMICs) face a significantly higher burden of premenopausal breast cancer, accounting for 55% of all cases. Mortality rates are also higher in LMICs, with 8.5 deaths per 100,000 women, compared to 3.3 per 100,000 in wealthier nations (3, 4). Compared with their older counterparts, young women with breast cancers are characterized by higher proportion of tumors with aggressive phenotypes and less favorable outcomes irrespective of stage at diagnosis (5).

In the United Arab Emirates (UAE) BC is the most common cancer, comprising approximately a third of all female cancers and remains the number one cause of cancer-related mortality (6). BC tends to be present earlier in the UAE population with a median age around 48 years and 21.5% of the BC cases are between age 30 and 40 years. BC has the largest burden of cancer in the UAE (7). The National Guidelines for Breast Cancer Screening and Diagnosis in the UAE recommend starting at age 40 years, with mammography to be done every 2 years (8). This conforms with the observations of most BC cases occurring in women in their 40s in the country. No screening guidelines recommend routine screening for average-risk women who are younger than 40 years, in view of a low BC incidence, unavailability of screening trials in this age subgroup, and poor performance characteristics of mammography. In a review of the results of 73,335 initial screening mammograms in women aged 35-39 years, the positive predictive value (PPV) was only 1.3% (9). However, in view of cancer cases still being commonly detected in women aged 30-40 years, it was previously proposed to perform screening in younger age (30 years and above) based on individualized risk assessment (7).

Recently, the blood-based biomarker hPG_{80} (circulating progastrin) has been shown to be a promising diagnostic biomarker for various types of solid cancers (10-16). In physiological conditions, progastrin is the precursor of the gastrointestinal hormone gastrin synthetized by antrum G cells and processed into gastrin during digestion (17). In pathological conditions, the GAST gene, which encodes progastrin, is a direct target of oncogenic pathways frequently activated in various types of cancers such as the APC/β-catenin or Ras pathways (18, 19). In these cancer cells, progastrin is not processed into gastrin and is released intact. Once released into the blood stream, circulating progastrin is named hPG_{80} to distinguish it from the precursor of gastrin. Many studies have demonstrated that hPG_{80} plays important roles in various pathological processes including cell proliferation, disruption of cell junctions, inhibition of apoptosis, survival of cancer stem cells and angiogenesis (20-29). High hPG_{80} concentrations have been reported in various types of cancers including early-stage breast cancer at a median age of 65 years (12). Therefore, we decided to evaluate for the first time the diagnostic value of hPG_{80} in young women with breast cancer in a monocentric prospective clinical trial at the University Hospital of Sharjah in UAE.

Patients and Methods

hPG_{80} level measurements in the blood samples. The ELISA DxPG80.lab kit (Biodena Care, Grabels, France) was used to measure hPG_{80} levels in plasma samples according to the manufacturer's instructions as described previously (30). The analytical performances of the kit have been described in Cappellini *et al.* (30). Briefly, the limit of quantitation (LoQ) was 3.3 pM and the upper limit of normal (ULN) was 10.9 pM. The inter- and intra-assay coefficients of variation (CV%) were <10%. No cross-reactivity was detected with gastrin-17, gastrin–Gly, or

C-terminus flanking peptide. No cross-reactivity was detected with other blood biomarkers, such as cancer antigen 125, carcinoembryonic antigen, or prostate-specific antigen. No interference was detected with chemicals, such as SN-38 and 5-fluorouracil, or with triglycerides, cholesterol, or hemoglobin.

Patients with breast cancer. EDTA plasma samples from 50 treatment-naïve patients with breast cancer including 21 patients below the age of 46 years, prospectively collected at diagnosis, between 2023 and 2024, were obtained from the University Hospital of Sharjah. All patients signed informed consent forms, and the study was approved by the local research ethics committee (UHS-HERC-139-23072023).

Asymptomatic individuals. EDTA plasma samples (n=47) from asymptomatic individuals below the age of 45 years, prospectively collected between 2023 and 2024, were obtained from the University Hospital of Sharjah. All patients signed informed consent forms, and the study was approved by the local research ethics committee (UHS-HERC-139-23072023). EDTA plasma samples (n=78) from asymptomatic individuals above the age of 45 years, prospectively collected between 2023 and 2024 were obtained from Balsam Health Services. All individuals signed informed consent forms.

Statistical analysis. Data is expressed as median±interquartile range (IQR) and mean±standard error of the mean (SE). Differences in hPG_{80} levels were evaluated using the non-parametric Mann-Whitney *U*-test. The diagnostic discriminative accuracy of hPG_{80} levels in patients with cancer compared to healthy subjects was assessed using Receiver Operating Characteristics (ROC) curve analyzes. Prism software (GraphPad Prism version 9.4, Dotmatics, Boston, MA, USA) was used to perform all the statistical analysis and to create figures. Correlations were performed with Spearman's rank correlation coefficient. The level of significance was set at $p<0.05$.

Results

Clinical characteristics. The study enrolled 50 patients with breast cancer including 21 patients below 46 years, 78 age-matched asymptomatic individuals [median age 53 years (range=28-74 years) *vs.* 51 years (range=45-76 years) respectively, $p=0.47$, Table I] and 47 asymptomatic individuals with an age below 45 years (median age 35 years; range=25-44 years, Table I).

Among the patients with breast cancer, 42/50 (84%) had invasive ductal carcinoma, 3/50 (6%) inflammatory breast cancer, 2/50 (4%) invasive lobular carcinoma, 2/50 (4%) mixed invasive ductal and lobular carcinoma and 1/50 (2%) invasive micropapillary carcinoma. 44/50 (88%) were estrogen receptor positive, 33/50 (66%) were HER2 positive, 36/50 (72%) were progesterone receptor positive, 18/50 (36%) had lymphovascular invasion, 25/50 (50%) had ductal carcinoma in situ and 31/50 (62%) had cancer on the right breast. Univariate analysis of hPG_{80} revealed no significant differences across breast cancer subtypes or hormonal status (Table II). In asymptomatic individuals, no correlation was observed between hPG_{80} levels and age in the cohort > 45 years of age and a weak negative correlation in the cohort <45 years of age (Spearman coefficient r=0.070 and r=–0.271, respectively, Figure 1A and B). In patients with breast cancer, a weak positive correlation between hPG_{80} levels and age was observed in the whole cohort and a moderate positive correlation in the cohort <45 years of age (Spearman coefficient r=0.276 and r=0.447, Figure 1C and D). No correlation was observed between hPG_{80} levels and %Ki67 or body mass index in patients with breast cancer (Spearman coefficient r=0.064, and r=0.050, Figure 1E and F, respectively). Finaly, we observed a tendency of higher hPG_{80} levels in invasive ductal carcinoma (IDC) compared to the other BC subtypes (median hPG_{80} 3.62 pM *vs.* 2.07 pM, $p=0.33$, respectively).

hPG_{80} Levels in patients with breast cancer, asymptomatic individuals and diagnostic performance. Plasma hPG_{80} levels in patients with breast cancer and asymptomatic

Table I. *Demographic and clinical characteristics of breast cancer patients and asymptomatic individuals.*

	All Breast cancer patients N (%)	Breast cancer patients <46 yo N (%)	Asymptomatic individuals >45 yo N (%)	Asymptomatic individuals <45 yo N (%)
No. of patients/individuals	50	21	78	47
hPG80				
Median (IQR), pM	3.55 (1.38-4.89)	2.24 (0.87-4.09)	1.66 (0.00-3.39)	1.66 (0.00-2.47)
Age				
Median (range), years	53 (28-74)	40 (28-46)	51 (45-76)	35 (25-44)
Estrogen receptor			N/A	
Negative	6 (12%)	3 (14.3%)		
Positive	44 (88%)	18 (85.7%)		
HER2				
Negative	33 (66%)	13 (61.9%)		
Positive	12 (24%)	7 (33.3%)		
Unknown	5 (10%)	1 (4.8%)		
Progesterone receptor				
Negative	13 (26%)	5 (23.8%)		
Positive	36 (72%)	16 (76.2%)		
Unknown	1 (2%)	0 (0%)		
TNBC				
Yes	5 (10%)	3 (14.3%)		
No	45 (90%)	18 (85.7%)		
Lymphovascular invasion				
Present	18 (36%)	9 (42.7%)		
Absent	31 (62%)	11 (52.5%)		
Unknown	1 (2%)	1 (4.8%)		
Ductal carcinoma *in situ*				
Present	25 (50%)	13 (61.9%)		
Absent	23 (46%)	7 (33.3%)		
Unknown	2 (4%)	1 (4.8%)		
Grade Notthingham				
I	6 (12%)	2 (9.6%)		
II	18 (36%)	6 (28,5%)		
III	25 (50%)	12 (57.1%)		
Unknown	1 (2%)	1 (4.8%)		
Positive lymph nodes				
Present	27 (54%)	8 (38.1%)		
Absent	23 (46%)	13 (61.9%)		
Location				
Left	18 (36%)	7 (33.3%)		
Right	31 (62%)	14 (66.7%)		
Both	1 (2%)	0 (0%)		
Breast cancer subtypes				
Invasive ductal carcinoma (IDC)	42 (84%)	18 (85.6%)		
Inflammatory (IBC)	3 (6%)	0 (6%)		
Invasive lobular carcinoma (ILC)	2 (4%)	1 (4.8%)		
Invasive micropapillary carcinoma (IMC)	1 (2%)	0 (2%)		
Mixed invasive ductal and lobular carcinomas (IDC-Ls)	2 (4%)	2 (9.6%)		

individuals are shown in Figure 2A. hPG_{80} levels were found to be significantly higher in patients with breast cancer than in asymptomatic individuals (median: 3.55 pM, IQR=1.38-4.89 *vs.* 1.66 pM, IQR=0.00-3.51, p=0.0006, respectively). Next, we conducted ROC curve analysis to assess the performance of hPG_{80} in differentiating

Table II. *Univariate analysis of plasma hPG_{80} levels by breast cancer subtypes and hormonal status.*

	hPG_{80}, median (IQR), pM	*p*-Value
Estrogen receptor		
Negative	3.55 (2.33-5.68)	
Positive	3.55 (1.18-5.03)	0.74
HER2		
Negative	3.47 (1.22-5.40)	
Positive	3.96 (1.51-5.18)	0.67
Progesterone receptor		
Negative	2.64 (1.03-3.78)	
Positive	3.81 (1.38-5.00)	0.27
TNBC		
Yes	2.64 (1.03-3.78)	
No	3.81 (1.38-5.00)	0.75
Lymphovascular invasion		
Present	2.53 (1.38-4.52)	
Absent	3.84 (1.05-5.05)	0.59
Ductal carcinoma *in situ*		
Present	3.50 (1.50-4.60)	
Absent	2.60 (0.70-6.65)	0.72
Grade Nottingham		
I	1.70 (1.23-3.60)	
II	3.00 (0.98-4.89)	
III	3.80 (1.50-7.15)	0.33
Positive lymph nodes		
Present	3.80 (1.40-7.60)	
Absent	3.50 (1.40-4.60)	0.48
Location		
Left	4.07 (1.53-6.23)	
Right	3.35 (0.98-4.84)	0.14
Breast cancer subtypes		
Invasive ductal carcinoma (IDC)	3.62 (1.38-5.40)	
Others	2.07 (1.14-4.24)	0.33

between patients with breast cancer and asymptomatic individuals. As shown in Figure 2B, the AUC value was 0.68 (95%CI=0.58-0.77; p=0.0008). Using a cut-off value based on the limit of quantification (LoQ) of the kit (3.3 pM), we found a sensitivity of 56%, a specificity of 72.5%, a negative predictive value (NPV) of 72.5% and PPV of 56%, to differentiate patients with breast cancer and asymptomatic individuals.

Comparative analysis of hPG_{80} levels in young breast cancer patients and asymptomatic individuals and diagnostic performance. Plasma hPG_{80} levels in breast cancer patients and asymptomatic individuals below 46 years old are shown in Figure 3A. hPG_{80} levels were found to be significantly higher in breast cancer patients than in asymptomatic individuals (median: 2.24 pM, IQR=0.87-4.09 *vs.* 1.66 pM, IQR=0.00-2.47, p=0.0425, respectively). Next, we conducted ROC curve analysis to assess the performance of hPG_{80} for differentiating between breast cancer patients and asymptomatic individuals. As shown in Figure 3B, the AUC value was 0.65 (95%CI=0.50-0.80; p=0.0443). Using a cut-off value based on the limit of quantification (LoQ) of the kit (3.3 pM), we found a sensitivity of 47.6%, a specificity of 89.4%, a NPV of 79.2% and PPV of 66.7%, to differentiate early age breast cancer patients and asymptomatic individuals.

Discussion

Currently, no blood-based biomarkers are available to effectively detect breast cancer in asymptomatic young women. In this study, we demonstrated that plasma hPG_{80} levels were significantly higher in patients with breast cancer compared to asymptomatic individuals – and this was also observed specifically in women under the age of 45 years. Notably, 57% of these patients had hPG_{80} levels above the LOQ, compared to only 13% of asymptomatic individuals.

Currently, the most widely used biomarkers for diagnosing breast cancer include hormone receptors (ER, PR and HER2), and the Ki-67 proliferation marker (31). These biomarkers are identified through tissue biopsies using immunohistochemistry or fluorescence in situ hybridization. Ki-67, a marker of cell proliferation, is used to assess the aggressiveness of the tumor, helping clinicians determine prognosis. These biomarkers are integral in categorizing breast cancer subtypes and influencing treatment plans, as they provide critical information on tumor biology. However, these biomarkers have limitations when it comes to diagnostic accuracy. For example, the presence or absence of ER, PR, and HER2 can vary between different areas of the same tumor or change over time, leading to potential diagnostic inconsistencies (32). This heterogeneity makes it challenging to rely solely on these biomarkers for an accurate diagnosis, especially

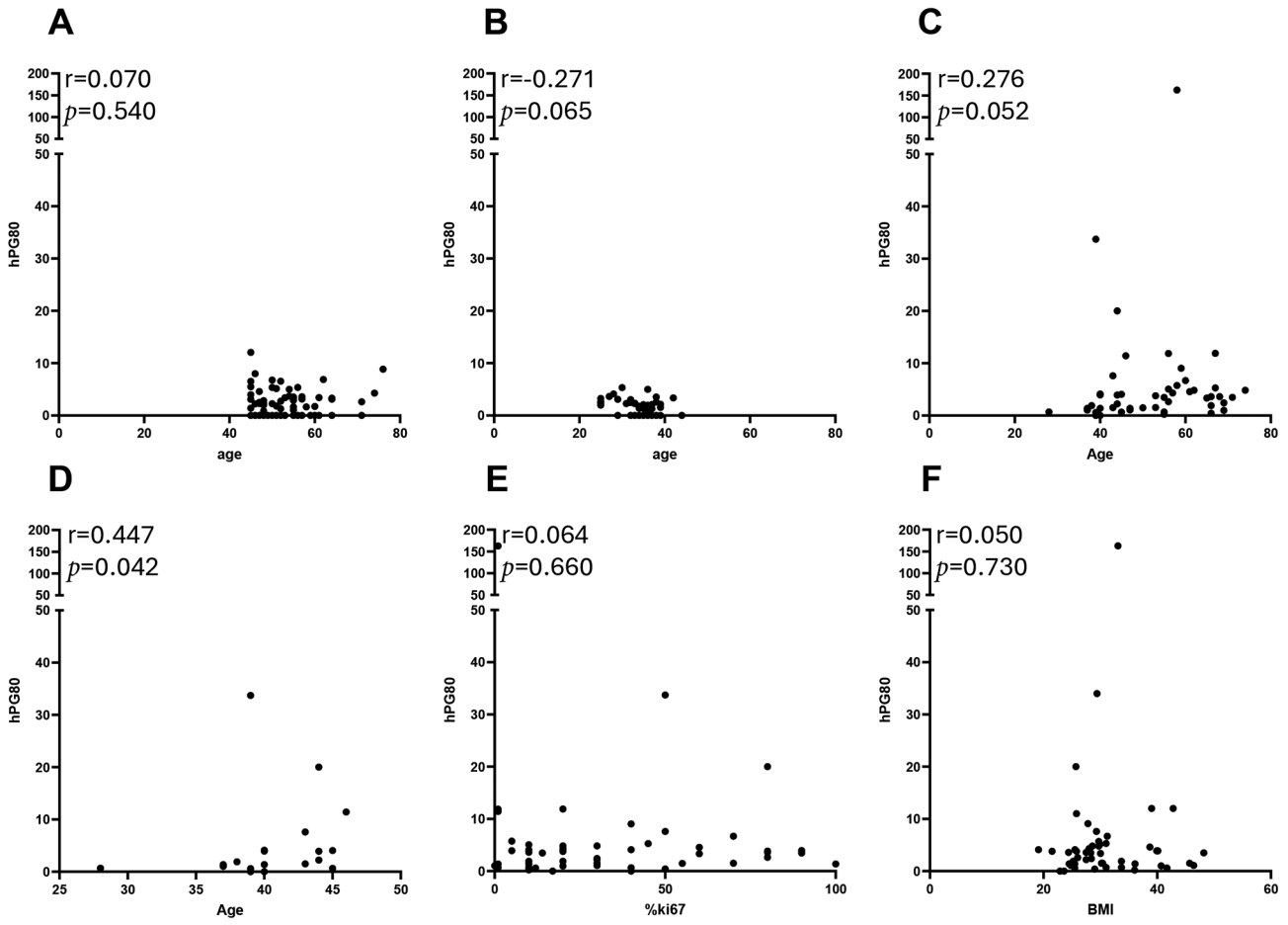

Figure 1. *Correlation analysis of plasma hPG_{80} levels in patients with breast cancer and asymptomatic individuals. (A) Correlation between age and hPG_{80} levels in asymptomatic individuals >45 years of age (n=78). (B) Correlation between age and hPG_{80} levels in asymptomatic individuals <45 years of age (n=47). (C) Correlation between age and hPG_{80} levels in patients with breast cancer (n=50). (D) Correlation between age and hPG_{80} levels in patients with breast cancer (n=50). (E) Correlation between %Ki67 and hPG_{80} levels in patients with breast cancer (n=50). (F) Correlation between BMI and hPG_{80} levels in patients with breast cancer (n=50).*

in cases where the tumor may not exhibit typical patterns. Ki-67, while useful for gauging tumor aggression, can be subject to interpretation variability, as different laboratories may use different scoring systems (32). Interestingly we found no correlation between hPG_{80} levels and Ki-67 showing that they are involved in different biological processes. Furthermore, these biomarkers are typically assessed after a biopsy or surgery, meaning they are not effective for early screening or diagnosing breast cancer at its earliest stages. Emerging biomarkers, such as circulating tumor DNA (ctDNA) and microRNAs, are being explored to overcome these limitations and offer more accurate, non-invasive methods for early detection and diagnosis of breast cancer (33).

The hPG_{80} gene is the direct target of the WNT/β-catenin pathway - a pathway involved in tumorigenesis in multiple organs. The WNT/β-catenin pathway is associated with pluripotency, self-renewal of stem cells, and differentiation; however abnormal activation of the pathway promotes activation of cancer stem cell progression and hence, metastasis (21, 29). Wnt signaling is often altered in breast cancer through genetic and

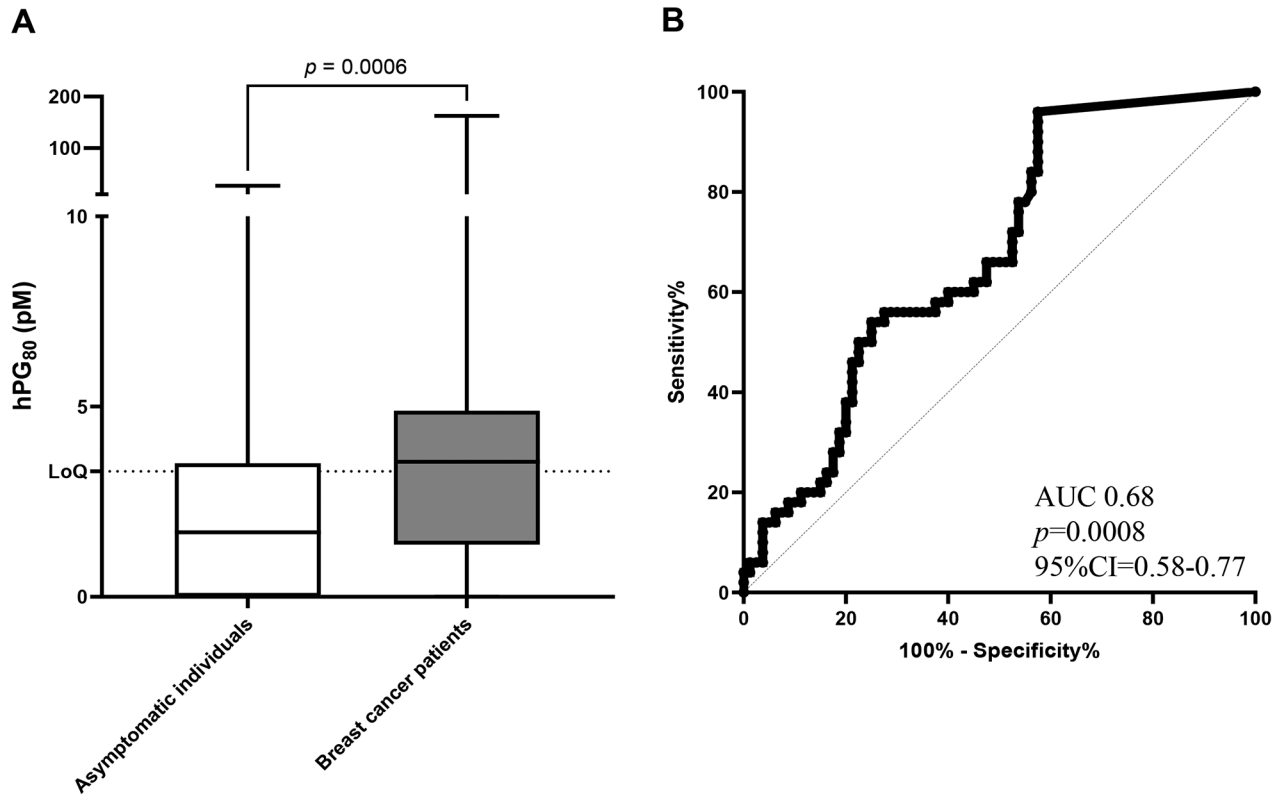

Figure 2. *Plasma hPG_{80} levels in patients with breast cancer and asymptomatic individuals. (A) Box-whisker plots show hPG_{80} levels in patients with breast cancer (n=50) and asymptomatic individuals (n=78). (B) Receiver operating characteristic curves (ROC) of hPG_{80} in differentiating patients with breast cancer from asymptomatic individuals. Boxes represent the interquartile range, and the horizontal line across each box indicates median values. The statistical differences were evaluated with the Mann-Whitney U-test. LoQ: Limit of quantification; AUC: area under the curve; 95%CI: 95% confidence interval.*

epigenetic changes, including mutations, amplifications, and methylation (34). While CTNNB1 (β-catenin) mutations are rare, Wnt activation is crucial for tumor development, mainly due to epigenetic activation of Wnt and inactivation of Wnt inhibitors (35). Furthermore, Wnt receptors are often overexpressed, especially in basal-like breast cancer (BLBC) and triple-negative breast cancer (TNBC) (36), leading to increased β-catenin stability and nuclear signaling and therefore potential hPG_{80} secretion. Moreover, Wnt signaling plays a key role in classifying breast cancer into histological and molecular subtypes. IDC shows regular β-catenin expression, while invasive lobular carcinoma lacks this expression, correlating with IDC's worse prognosis (37).

Study limitations. First, the small number of patients enrolled in the study can limit the power of statistical analysis. Second, this study is a single-center study that might require external validation to confirm these promising results.

Conclusion

This prospective study is the first to demonstrate that hPG_{80} may serve as a useful blood-based biomarker to aid in the screening of breast cancer in young, high-risk women, particularly when used in combination with imaging. While these findings are promising, they require validation in larger-scale cohorts to confirm their clinical utility and

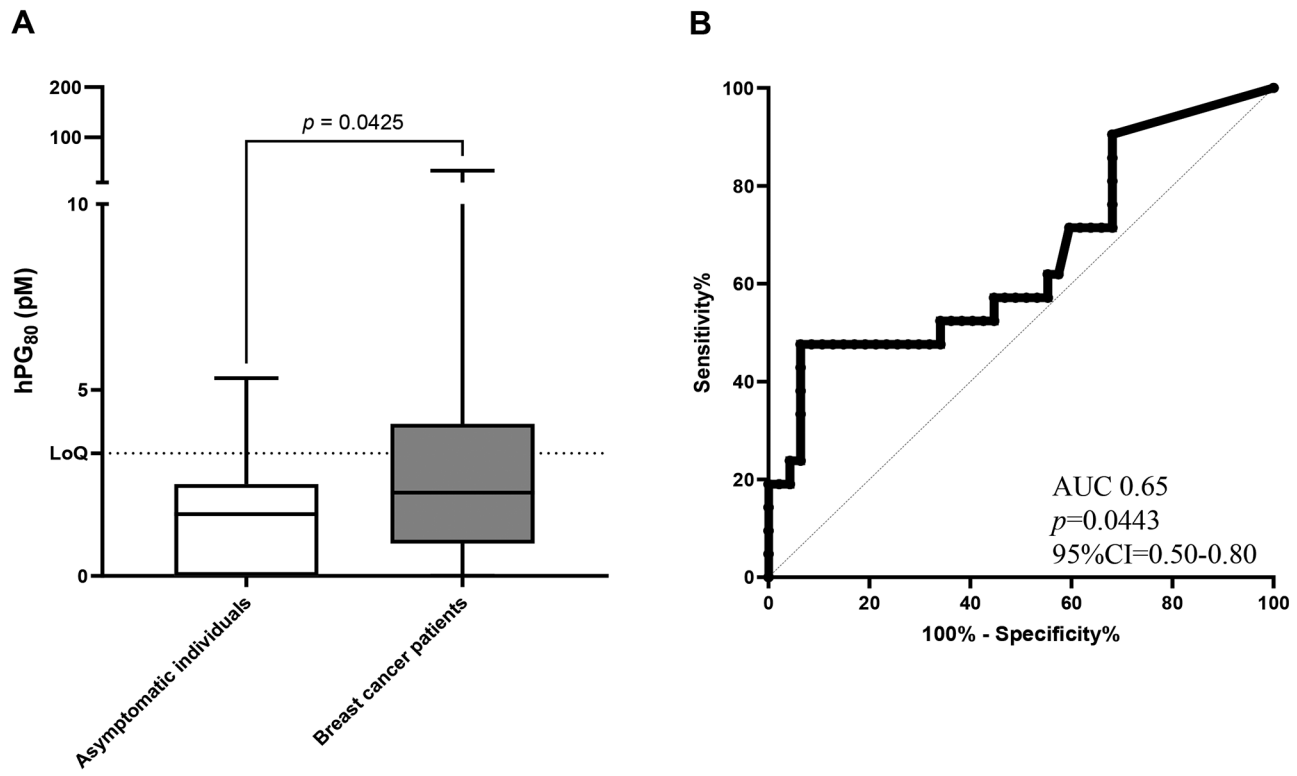

Figure 3. *Plasma hPG_{80} levels in patients with breast cancer and asymptomatic individuals under the age of 45. (A) Box-whisker plots show hPG_{80} levels in patients with breast cancer (n=21) and asymptomatic individuals (n=47). (B) Receiver operating characteristic curves (ROC) of hPG_{80} in differentiating patients with breast cancer from asymptomatic individuals. Boxes represent the interquartile range, and the horizontal line across each box indicates median values. The statistical differences were evaluated with the Mann-Whitney U-test. LoQ: Limit of Quantification; AUC: area under the curve; 95%CI: 95% confidence interval.*

further support the early detection of breast cancer in young women.

Conflicts of Interest

AP is Chief Scientific Officer of Progastrin Manufacturing. DJ is senior scientist consultant of Progastrin Manufacturing. All other Authors: no conflicts of interest.

Authors' Contributions

AP, DJ, RB wrote the manuscript. AP, DJ, RB analyzed the data. RB contributed to the recruitment of patients. RB is the principal investigator.

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Artificial Intelligence (AI) Disclosure

During the preparation of this manuscript, a large language model (ChatGPT, OpenAI) was used solely for

language editing and stylistic improvements in select paragraphs. No sections involving the generation, analysis, or interpretation of research data were produced by generative AI. All scientific content was created and verified by the authors. Furthermore, no figures or visual data were generated or modified using generative AI or machine learning–based image enhancement tools.

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