Applied Medical Informatics
Research Letter Vol. 47, No. 2/2025, pp: 42-48

# Discovery of a Sinusoidal Pattern in the Cancer Antigen 15-3 Time Series of a Patient with Metastatic Breast Cancer

**Alexandros CLOUVAS**

Department of Electrical and Computer Engineering, Aristotle University of Thessaloniki, Egnatia Street, GR-54124 Thessaloniki, Greece.
E-mail: clouvas@ece.auth.gr

**Received: 30 January 2025/Accepted: 17 May 2025/ Published online: 24 May 2025**

**Abstract**
Cancer Antigen 15-3 (CA 15-3) is a glycoprotein commonly linked to breast cancer. Monitoring CA 15-3 levels is crucial for tracking disease progression and evaluating treatment response in patients with metastatic breast cancer. Although fluctuations in CA 15-3 levels are common in patients with metastatic breast cancer, no periodic pattern has been identified to date. In this study, a sinusoidal pattern was observed for the first time in CA 15-3 time-series data of a patient with metastatic breast cancer. This pattern recurred every 175 days, from February 2024 to January 2025. Statistical analysis strongly indicated that the observed sinusoidal variation was highly unlikely to have occurred by chance, thus providing an excellent fit to the data. This finding is both novel and captivating, as changes in CA 15-3 levels are usually linked to disease progression or treatment responses rather than following a predictable sinusoidal rhythm.

**Keywords:** Time-series; Cancer Antigen CA 15-3 (CA 15-3); Male breast cancer; Sinusoidal model.

## Introduction

Breast cancer is the most common cancer among women worldwide. Over the past two decades, increased public awareness and advancements in breast imaging technologies have significantly improved early diagnosis and screening, leading to better prognosis [1, 2]. In contrast, male breast cancer is a rare and poorly understood disease, accounting for approximately 1% of all breast cancer cases in the Western world. However, its incidence has been steadily increasing in recent decades [3, 4]. Although female and male breast cancers share many similarities, the rarity of male breast cancer presents significant challenges in terms of awareness, early detection, and treatment.

Cancer Antigen 15-3 (CA 15-3) is a glycoprotein found in benign and malignant breast diseases as well as in breast cancer with liver or bone metastases. Cancer Antigen 15-3 was initially identified as a potential marker of breast cancer in the 1980s [5]. Since its discovery, extensive research has been conducted, leading to its widespread use in clinical practice as a tumor marker for breast cancer [6,7]. However, current guidelines [8-10] discourage the serial measurement of CA 15-3 in the follow-up of patients with early breast cancer due to insufficient evidence demonstrating a survival benefit. Despite these guidelines, many oncologists routinely conduct serial assessments of blood-based tests for CA 15-3 as part of the standard follow-up for asymptomatic patients with early breast cancer. Ryu et al. [6] analyzed changes in CA 15-3 levels in over 11,000 patients with breast cancer, revealing a significant association between elevated CA 15-3 levels within the normal range and disease recurrence. This association was observed across all the molecular subtypes. De Cock et al. [7] reported that the systematic use of CA 15-3 in patient follow-up led to the diagnosis of metastatic disease in 37% of cases owing to rising CA 15-3 levels.

It is important to emphasize that a primary role of CA 15-3 is in monitoring therapy in patients with metastatic breast cancer. Measuring CA 15-3 levels is particularly useful for evaluating disease progression and assessing the

treatment response in these patients [11]. However, CA 15-3 should not be used in isolation but rather in conjunction with diagnostic imaging, clinical history, and physical examination.

This study analyzed plasma CA 15-3 levels in a male patient with metastatic breast cancer, monitored from April 14, 2020, to January 9, 2025. A sinusoidal pattern was observed in the CA 15-3 time-series data for the first time between February 2024 and January 2025. While fluctuations and nonlinear trends in cancer biomarkers (such as CA 15-3) have been observed—often attributed to treatment effects, tumor dynamics, or biological variability—a regular sinusoidal pattern, defined as a mathematically periodic rise and fall over time, has not, to the best of our knowledge, been reported in peer-reviewed research to date. The aim of this research letter was to document and statistically verify the unexpected finding of a sinusoidal pattern in CA 15-3 levels in a patient with metastatic breast cancer, with the objective of bringing it to attention and encouraging further investigation into potential biological or clinical significance.

## Materials and Methods

### *Medical History of the Patient*

The medical history of this 70-year-old male patient has been previously described [12]. In summary, he underwent a right mastectomy for a malignant tumor on April 27, 2020. Thirty-seven months later, on May 18, 2023, elevated CA 15-3 levels (37.2 U/mL) were detected. A Positron Emission Tomography/Computed Tomography (PET/CT) scan performed on August 11, 2023, confirmed metastatic breast cancer in the left trochanteric region. The cancer was classified as grade 3 according to the Elston and Ellis system [13], with estrogen receptor (ER) and progesterone receptor (PR) positivity, 20% HER2 expression, and Ki-67 index of 30%. The medical team at the "Theagenio" Cancer Hospital in Thessaloniki, Greece initiated the following treatment: Letrozole (2.5 mg) with palbociclib (125 mg). Two monthly injections of XGEVA (120 mg) and ARVEKAP (3.75 mg). Radiotherapy (10 sessions of 3 Gy each) was preceded by prophylactic threading using a long-gamma nail on September 13, 2023.

### *Time Series of CA 15-3 and Data Analysis*

Plasma CA 15-3 levels were monitored through regular blood tests over a period of five years. A total of 41 tests were conducted between April 14, 2020, and January 9, 2025, across two laboratories. The normal reference range for CA 15-3 is typically less than 30 U/mL; however, this value may vary slightly depending on the laboratory and testing method used. The first laboratory utilizes the enhanced chemiluminescence immunoassay technique with a reference value of <30 U/mL, whereas the second laboratory employs the microparticle chemiluminescence immunoassay technique, using a reference value of <31.3 U/mL. To ensure accuracy, measurements were cross validated three times by performing tests at both laboratories within a maximum interval of two days between paired tests. Discrepancies in results between the two laboratories were observed at rates of 11.3%, 1.9%, and 3.6%, respectively.

This study focuses on analyzing sixteen CA 15-3 measurements collected from February 2024 to January 2025. To model the CA 15-3 values, the following general sinusoidal function was applied:

$$f(t) = A \times \sin(B \times t + C) + D \quad (1)$$

where: t: Time in days since February 8, 2024; A: Amplitude (height of peaks from baseline in U/mL); B: Angular Frequency (rate of change of the angle in radians per day); C: Phase shift (alignment of the pattern in radians); D: Baseline level (average CA 15-3 concentration in U/ml). Most computations were conducted using Wolfram Mathematica on the Wolfram Cloud platform [14], with some analyses performed in Python [15] using appropriate numerical and statistical libraries. The parameters A, B, C, and D of the sinusoidal function, along with their corresponding errors, were estimated by performing a nonlinear model fit using the built-in NonlinearModelFit function in Wolfram Mathematica on the Wolfram Cloud platform. This function performs nonlinear least squares fitting using iterative numerical optimization algorithms. In the background, NonlinearModelFit typically uses the Levenberg–Marquardt algorithm for estimating model parameters. The standard errors reported for the parameters typically represent one standard deviation (1σ), assuming the residuals are normally distributed. The quality of the

fit was evaluated by calculating the squared correlation coefficient ($R^2$) and the p-values for parameters A, B, C, and D using Wolfram Mathematica. The period of the sinusoidal function obtained from the fit was compared with that independently determined through Fast Fourier Transform (FFT) analysis, also performed in Wolfram Mathematica. Although the original data points were recorded at irregular time intervals, the FFT which assumes uniformly sampled data was applied by approximating the data as regularly spaced. This was achieved by calculating the mean of the differences between consecutive x-values and using it as the effective sampling interval. By treating the data as uniformly spaced with this average interval, frequency components were estimated, allowing the FFT to be used despite the irregular sampling. Additionally, a residual analysis was conducted with residuals defined as the difference between the observed and predicted values. Statistical analysis of residuals helps ensure that the sinusoidal model is valid, reliable, and not misleading. It is a diagnostic step to verify that the sinusoidal model captures the real signal and that any remaining "noise" is truly just noise. To statistically assess whether the residuals could be considered random variations, the following statistical tests were performed in Python using appropriate statistical libraries:

- Autocorrelation Analysis (Ljung-Box Test). This test checks if the residuals are correlated over time (i.e., if there are hidden patterns).
- Normality Test (Shapiro-Wilk Test). This test determines if the residuals follow a normal distribution, a common assumption for random noise.
- White Noise Test (Runs Test for Randomness). This test checks if the sequence of positive and negative residuals occurs in a random pattern.

## Results and Discussion

Figure 1 presents the time-series measurements of the CA 15-3 levels. The CA 15-3 trend can be divided into three distinct periods:

1. **Stable Period Before Recurrence**: During this phase, prior to recurrence, CA 15-3 levels remained relatively stable with small random fluctuations.
2. **Drastic Changes Due to Metastasis and Treatment**: This phase is marked by a continuous and significant increase in CA 15-3 levels, attributed to metastasis in the trochanter. This was followed by a sharp decline in response to the treatment mentioned earlier, which is still ongoing today.
3. **Fluctuation Period (February 2024 to January 2025):** Since February 2024, CA 15-3 levels have fluctuated between 25 U/mL and 41 U/mL, with an average of approximately 33.5 ± 4 U/mL. These fluctuations do not appear to be random; instead, they follow a distinct sinusoidal pattern, as shown in Figure 2.

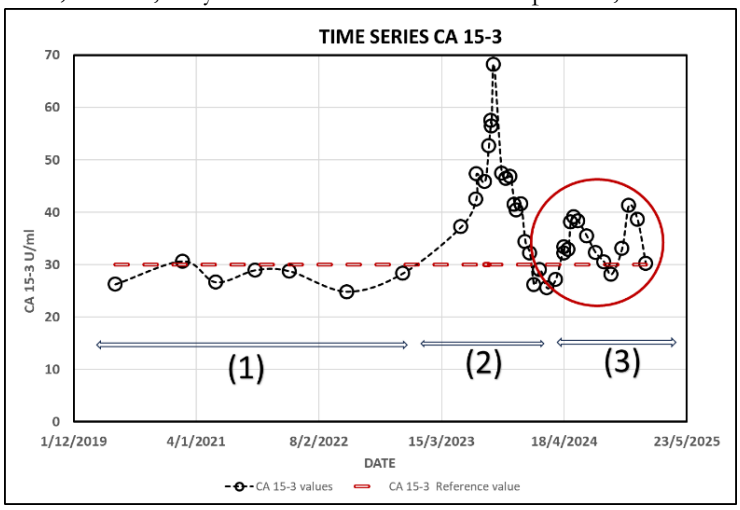


**Figure 1.** Time-series measurements of CA 15-3. The dashed line connecting the CA 15-3 values is included for visual guidance only.

Figure 2 presents sixteen CA 15-3 measurements collected from February 2024 to January 2025 (referred to as

period 3 in Figure 1). The dashed line in Figure 2 represents the fit analysis using a sinusoidal function (Equation2).

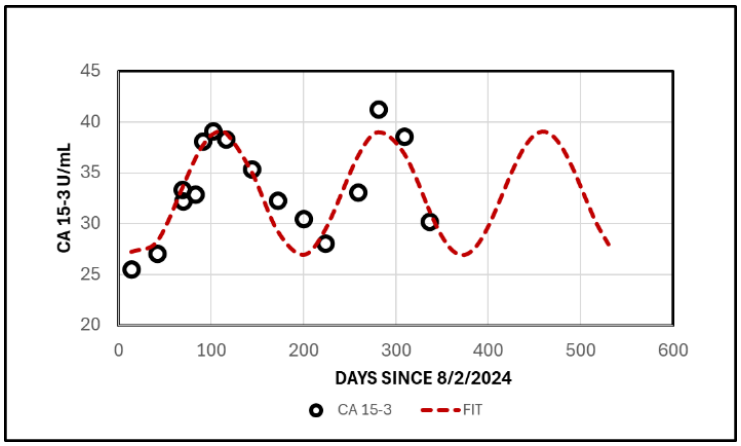


**Figure 2.** CA 15-3 measurements from February 2024 to January 2025 . The dashed line represents the sinusoidal fit (Equation 2).

The parameters A, B, C, and D of the sinusoidal function (Equation 1) fitted to the CA 15-3 values are presented in Table 1, along with the corresponding p-values for each parameter.

**Table 1.** Parameters A, B, C, and D of the sinusoidal function (Equation 1) fitted to the CA 15-3 values, along with the corresponding p-values for each parameter.

| Parameter | Value | p-value |
|---|---|---|
| Amplitude (A), U/mL | 6.06 ± 0.77 | $4.21\times10^{-6}$ |
| Angular Frequency (B), rad $d^{-1}$ | 0.036 ± 0.0013 | $2.08\times10^{-12}$ |
| Phase Shift (C), rad | −2.61 ± 0.24 | $1.64\times10^{-7}$ |
| Baseline Level (D), U/mL | 32.99 ± 0.57 | $4.67\times10^{-16}$ |

By substituting the values of parameters, A, B, C, and D into Equation 1, the resulting sinusoidal fit equation is:

$$f(t) = 6.06\times sin(0.036\times t-2.61)+32.99 \quad (2)$$

The value of B yields a period of $T = \frac{2\pi}{B}$, which corresponds to T≈175 d. This suggests that the pattern repeats approximately every six months. This result aligns with the Fast Fourier Transform (FFT) analysis of the measured CA 15-3 values. From the analysis, the dominant frequency was approximately 0.0058 $d^{-1}$, corresponding to a dominant period T≈173 d, which is very similar to the period deduced from the sinusoidal model. This close agreement supported the validity of the sinusoidal fit.

A squared correlation coefficient of 0.996 was obtained, indicating an excellent fit. All parameters (Amplitude, Angular Frequency, Phase shift, and Baseline Level) had extremely small p-values, indicating that each of them was statistically significant in contributing to the model's fit.

Even if the $R^2$ value is very high, it is essential to examine the residuals to ensure the accuracy of the model and identify any potential underlying patterns or biases. In Figure 3, the time dependence of the residuals is shown.

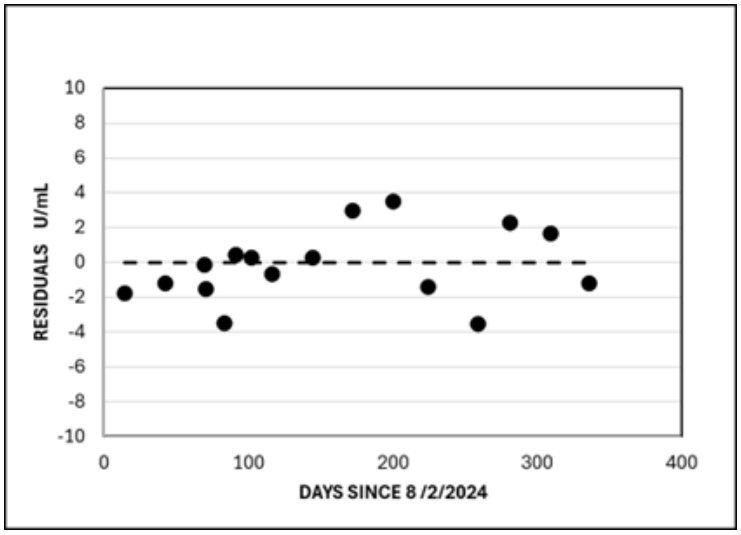


**Figure 3.** Time-dependent difference between the observed and predicted CA 15-3 values (residuals).

The mean of the residuals is approximately -0.192, which is close to zero, indicating that the model's predictions are generally unbiased, with no significant tendency to systematically over- or under-predict. The residuals include both positive and negative values and fluctuate without displaying a clear trend over time, suggesting that the model does not consistently overestimate or underestimate the data. To statistically evaluate whether the residuals represent random variation, several tests were performed. The p-value of the Ljung-Box test was 0.149, greater than the 0.05 threshold, indicating no significant autocorrelation. The Shapiro-Wilk test yielded a p-value of 0.652, suggesting that the residuals do not significantly deviate from a normal distribution. Additionally, the Runs test for randomness returned a p-value of 0.796, showing no evidence against the null hypothesis that the sequence is random. These results collectively indicate that the residuals exhibit no significant structure and can be considered random variation, thereby supporting the accuracy and robustness of the sinusoidal model

To the best of our knowledge, this is the first report of a sinusoidal pattern observed in the CA 15-3 time-series data of a male patient with metastatic breast cancer. While fluctuations and nonlinear trends in cancer biomarker levels—such as CA 15-3—have been previously reported [16], these variations are typically attributed to treatment effects, tumor dynamics, and individual biological variability. Despite these known influences, a consistently sinusoidal pattern—characterized by a mathematically regular and periodic rise and fall over time—has not been described in the peer-reviewed literature. The absence of such documentation suggests that this type of biomarker behavior may be rare, under-recognized, or potentially overlooked due to the prevailing focus on more abrupt or monotonic changes typically associated with disease progression or therapeutic response.

Despite the interest generated by this novel finding, it should not be interpreted uncritically. This study is limited by its single-patient design, which significantly restricts the generalizability of the results to broader patient populations. The fitting of a sinusoidal model to a limited number of data points raises concerns about potential overfitting. Moreover, the selection of a specific 12-month interval was not justified a priori, introducing the possibility of selection bias. The absence of a clearly defined biological or physiological mechanism to explain the observed periodicity further limits the clinical interpretability of the results. Although cross-validation of measurements was performed across two laboratories, subtle differences in assay procedures and inherent variability may have contributed to the observed oscillations. Additionally, unmeasured external factors—such as circadian or seasonal rhythms, subclinical conditions, or procedural inconsistencies—could have influenced the variability in CA 15-3 levels. Taken together, these limitations emphasize the exploratory nature of the study and underscore the need for validation in larger, multi-patient cohorts.

From a medical standpoint, the patient's treatment regimen remained unchanged throughout the study period (February 2024 to January 2025), and his overall health status was stable. Computed tomography (CT) scans performed twice during this interval showed no evidence of disease recurrence. Additionally, the baseline level (D) derived from the sinusoidal fit during this period was 32.99 ± 0.57 U/mL, which is close to the reference value of <31.3 U/mL used by the laboratory where most measurements were conducted. According to the oncologists

involved, although the observed sinusoidal pattern is unusual, it does not signal a negative clinical outcome, particularly given the patient's stable condition. It is of interest to explore whether the sinusoidal model proposed in this study can reliably predict future CA 15-3 levels. Early indications are promising. The fit shown in Equation 2 was based on CA 15-3 measurements up to January 9, 2025. Since then, four additional measurements have been obtained (from January 31 to April 2, 2025) and are presented in Figure 4. These new data points clearly follow the sinusoidal trend, supporting the predictive value of the model in this individual under stable clinical conditions.

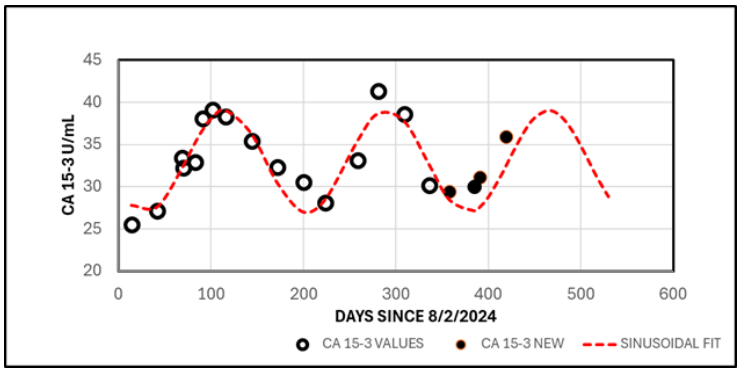


**Figure 4.** Same as Figure 2, with four additional measurements included after the model fitting was performed.

## Conclusions

This paper reports the first observation of a sinusoidal pattern in CA 15-3 concentrations in a patient with metastatic breast cancer, with a periodicity of approximately 175 days. Statistical modeling demonstrated an excellent fit to the data, supported by residual analysis and Fourier transformation. While this observation is novel and statistically compelling, it is based on an individual case and must be interpreted with caution. The absence of an identifiable biological mechanism, combined with the potential for the influence of measurement variability or unmeasured external effects, highlights the need for further study. Prospective monitoring of this patient may serve to assess the predictive value of the model over time, and the same time-series analyses in larger groups of patients would determine whether or not such patterns are reproducible or of clinical significance. Until such time, this observation must be considered hypothesis-generating and a starting point to further study of temporal dynamics in tumor marker behavior.

**List of Abbreviations:** CA 15-3: Cancer Antigen 15-3, PR: Progesterone Receptor, ER: Estrogen Receptor, HER2: Human Epidermal Growth Factor Receptor 2; PET/ CT: Positron Emission Tomography/Computed Tomography, FFT: Fast Fourier Transform.

**Author Contributions:** Not applicable, as there is only one author.

**Funding**: This research received no external funding.

**Ethics Statement:** Not applicable.

**Data Availability Statement**: The author declares that data supporting the findings of this study are available within the paper in form of figures. Additional details are available upon request.

**Acknowledgments:** The author would like to thank the medical staff of the Department of Clinical Oncology and Chemotherapy at Theagenio Cancer Hospital of Thessaloniki for the high-quality care provided during his treatment.

**Conflict of Interest:** The author declares no conflict of interest.

## References

1. Harbeck N, Gnant M. Breast cancer. Lancet. 2017;389:1134–1150. doi: 10.1016/S0140-6736(16)31891-8.
2. Akram M, Iqbal M, Daniyal M, Khan AU. Awareness and current knowledge of breast cancer. Biol Res. 2017;

50:33. doi: 10.1186/s40659-017-0140-9.
3. Abdelwahab Yousef AJ. Male breast cancer: epidemiology and risk factors. Semin Oncol. 2017;44:267-72. doi: 10.1053/j.seminoncol.2017.11.002.
4. Rizzolo P, Zelli V, Silvestri V, Valentini V, Zanna I, Bianchi S, et al. Insight into genetic susceptibility to male breast cancer by multigene panel testing: results from a multicenter study in Italy. Int J Cancer. 2019;145:390-400. doi: 10.1002/ijc.32106.
5. Gang Y, Adachi I, Ohkura H, Yamamoto H, Mizuguchi Y, Abe K. [CA 15-3 is present as a novel tumor marker in the sera of patients with breast cancer and other malignancies]. Gan To Kagaku Ryoho. 1985;12(12):2379-86. [Japanese]
6. Ryu JM, Kang D, Cho J, Lee JE, Kim SW, Nam SJ, et al. Prognostic Impact of Elevation of Cancer Antigen 15-3 (CA15-3) in Patients With Early Breast Cancer With Normal Serum CA15-3 Level. J Breast Cancer. 2023;26(2):126-35. doi: 10.4048/jbc.2023.26.e17.
7. De Cock L, Heylen J, Wildiers A, Punie K, Smeets A, Weltens C, Neven P, Billen J, Laenen A, Wildiers H. Detection of secondary metastatic breast cancer by measurement of plasma CA 15.3. ESMO Open. 2021;6(4):100203. doi: 10.1016/j.esmoop.2021.100203.
8. Cardoso F, Kyriakides S, Ohno S. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019;30:1194-220.
9. Harris L, Fritsche H, Mennel R. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol. 2007;25:5287-312.
10. Khatcheressian JL, Hurley P, Bantug E. Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013;31:961-5.
11. Duffy MJ, Evoy D, McDermott EW. CA 15-3: uses and limitation as a biomarker for breast cancer. Clin Chim Acta. 2010;411(23-24):1869-74. doi: 10.1016/j.cca.2010.08.039
12. Clouvas A. Exploring the Significance of Cluster Analysis on Time-Series Measurement of Plasma Cancer Antigen 15-3 in a Patient with Metastatic Breast Cancer. Appl Med Inform 2024;46(3):83-90.
13. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology. 1991;19(5):403-10. doi: 10.1111/j.1365-2559.1991.tb00229.x
14. Wolfram Research, Inc., Wolfram|Alpha Notebook Edition, Champaign, IL. 2024.
15. Python Software Foundation. 2023. Available from: https://www.python.org/
16. Tampellini M, Berruti A, Bitossi R, Gorzegno G, Alabiso I, Bottini A, et al. Prognostic significance of changes in CA 15-3 serum levels during chemotherapy in metastatic breast cancer patients. Breast Cancer Res Treat. 2006;98:241-8. doi:10.1007/s10549-005-9155-y