
Metastatic mammary carcinoma in a mature singleton placenta

Francia Victoria A. de los Reyes, MD^a and Arlene L. Santos, MD^b

^aPathology Laboratory, ^bDepartment of Pathology, College of Medicine

Abstract

Introduction Placental metastasis from maternal malignancies is a rare occurrence with a significantly adverse prognosis on the mother with no known effect or established risk factors for the newborn. As such, characterization of these lesions is necessary to serve as a stepping stone for more exhaustive studies regarding this presentation.

Case Summary This is a case of a metastatic breast carcinoma in a mature singleton placenta in a 39 year old woman diagnosed with invasive breast carcinoma of no special type/invasive ductal carcinoma, not otherwise specified, during the second trimester of pregnancy. Also discussed are the immunohistochemistry studies done to confirm the origin of the tumor. A comparison of the ER, PR, and HER2/neu receptor status between the primary lesion and the placental metastasis was also done.

Conclusion Pregnancy-associated breast cancer is a lesion that carries adverse prognosis for the mother because of the delay in diagnosis attributable to confusion of symptomatology. The pertinent problem in pregnancy-associated breast cancer with placental metastasis is the deficiency of the placenta to induce tumor metastasis away from itself.

Key words: Placental metastasis, metastatic breast carcinoma, pregnancy-associated breast carcinoma, immunohistochemistry

Breast cancer in pregnancy comprises 10% of diagnosed cases of breast cancer in women under

40 years, and is the second most common pregnancy-associated malignancy after cervical cancer.^{1,2} Although it is known that there is a significant adverse prognosis for the mother, no known established risks associated with the occurrence of placental metastasis have been described. Furthermore, no known risk factors for fetal extension or the lack thereof have been noted, and the impact of such on the newborn is likewise not known.³ As such, characterization of these lesions is necessary to serve as a stepping stone for more exhaustive studies regarding this presentation.

Correspondence:

Francia Victoria A. de los Reyes, MD, Pathology Laboratory, University of the East Ramon Magsaysay Memorial Medical Center, Aurora Boulevard, Barangay Doña Imelda, Quezon City 1113; Email: kaidelosreyes@gmail.com; Telephone +639479154451

2nd place, Oral Platform Presentation, Spring Scientific Meeting April 16-17, 2016, Hong Kong International Academy of Pathology, Prince of Wales Hospital, Hong Kong

The Case

This is the case of a 39 year old woman who presented with a left breast mass during the second trimester of pregnancy which was diagnosed as invasive ductal carcinoma/invasive carcinoma of no special type, left breast, by core needle biopsy. The patient subsequently also presented with a mass on the right breast during the third trimester of pregnancy, with no intervention done for both lesions, as per patient's choice, until the baby was delivered (Figure 1A). She underwent spontaneous delivery to a live full term girl at 36 1/7 weeks age of gestation, appropriate for gestational age, with a low birth weight of 2400 grams, Apgar score of 9 and 9 at 1 and 5 minutes. She also delivered a singleton discoid placenta with no identifiable gross lesions on delivery. The placenta was submitted for histopathologic evaluation. No other work-up was done regarding the patient's breast malignancy at this point as per the patient's prerogative.

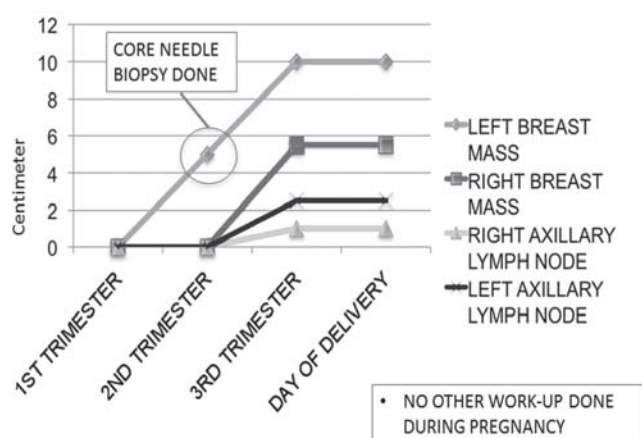


Figure 1A. Progression of the disease during pregnancy.

The core needle biopsy of the left breast mass was retrieved and reviewed for possible comparison if a metastatic lesion would be detected in the placenta. The tumor in the biopsy specimen showed cords, nests, and clusters with moderate degree of pleomorphism and anisonucleosis (Figure 1B-1C). Gross findings showed a singleton placenta with a tan to dark brown, firm, maternal surface with complete cotyledons. The fetal surface was gray to tan and smooth. The cord was paracentrally attached and had two arteries and one vein. Cut sections showed a homogenous dark brown surface. No grossly identifiable tumor area was noted in the entire specimen (Figure 2A-2C). Histologic findings from the placenta showed sections with small chorionic villi with well vascularized stroma. Distinctly noted were proliferations of malignant neoplastic cells as multiple focal lesions in the intervillous space, with no evidence of direct chorionic villi involvement. The tumor was organized in clusters and sheets with attempts at glandular formation. The cells had enlarged, pleomorphic nuclei, prominent nucleoli, and irregular nuclear membranes. Mitosis was noted at 18-20 figures/10 high power fields, and areas of atypical mitosis and tumor necrosis were seen. The tumor was seen insinuating in the intervillous space with no extension into the fetal villous space (Figure 3A-3D). The umbilical cord and the chorioamnionic membranes showed no tumor involvement (Figure 3E). Thus, the diagnosis of metastatic mammary carcinoma in a mature singleton placenta was made, with strong correlation with the history of invasive breast carcinoma. The carcinoma was limited to the maternal intervillous component of the placenta, with no extension to the chorioamnionic membranes, and to the vessels and matrix of the umbilical cord.

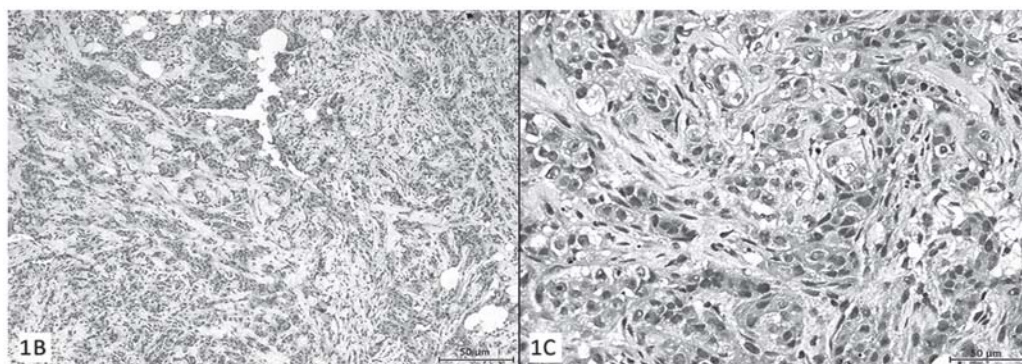


Figure 1B. Microscopic findings of the core needle biopsy, left breast. (50x magnification)

Figure 1C. Microscopic findings of the core needle biopsy, left breast. (400x magnification)



Figure 2A. Gross specimen of the maternal surface of the placenta with the corresponding dimensions

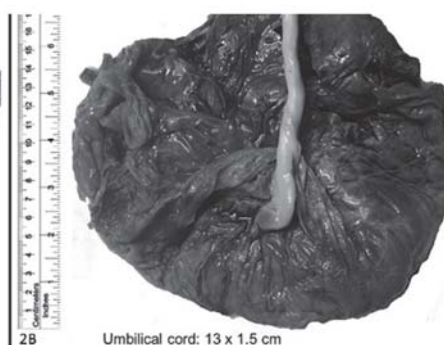


Figure 2B. Gross specimen of the fetal surface placenta and umbilical cord with the corresponding dimensions

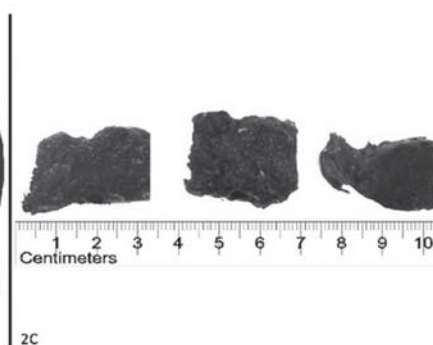


Figure 2C. Cut sections of the placental parenchyma

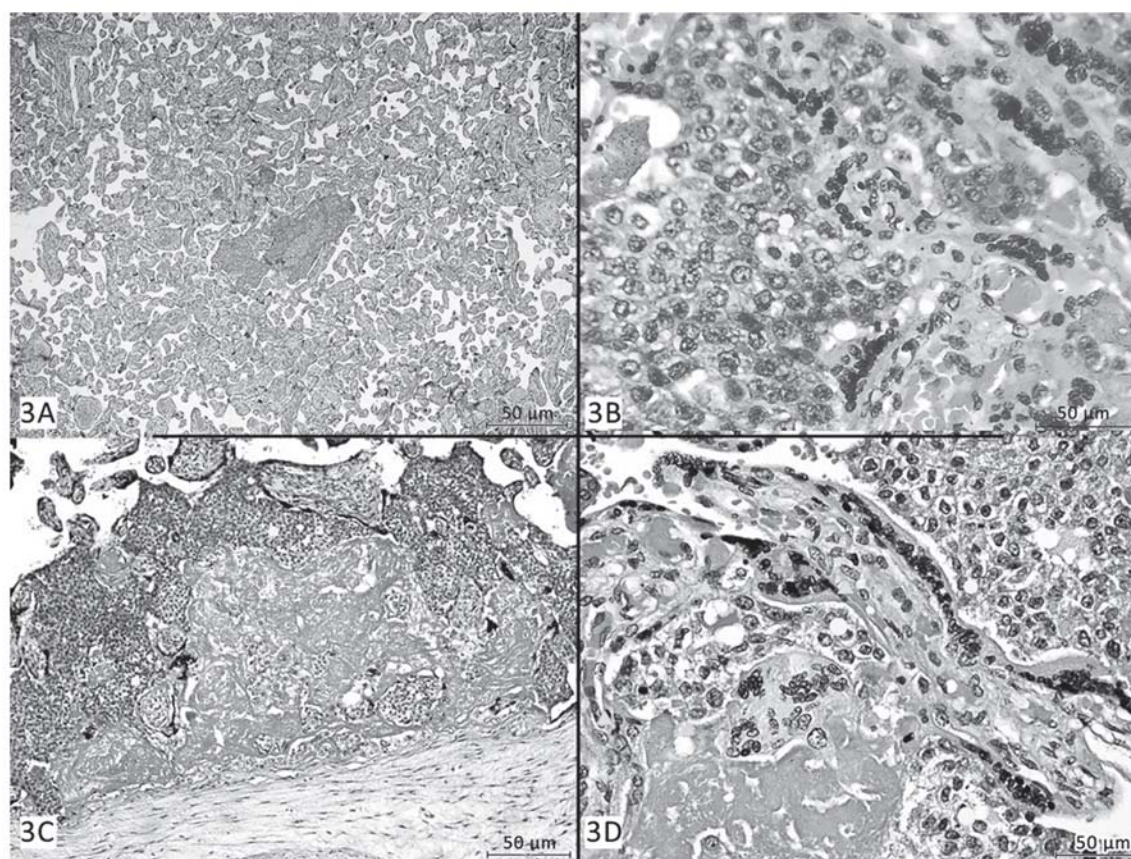


Figure 3A. Metastatic tumor cells surrounded by mature chorionic villi. (50x magnification)

Figure 3B. Metastatic tumor cells adherent to the trophoblastic cells of the chorionic villi. green triangle - chorionic villi; yellow circle - tumor cells. (400x magnification)

Figure 3C. Metastatic tumor cells confined to the intervillous space. green triangle - chorionic villi; yellow circle - tumor cells. (100x magnification)

Figure 3D. Metastatic tumor cells confined to the intervillous space. green triangle - chorionic villi; yellow circle - tumor cells. (400x magnification)

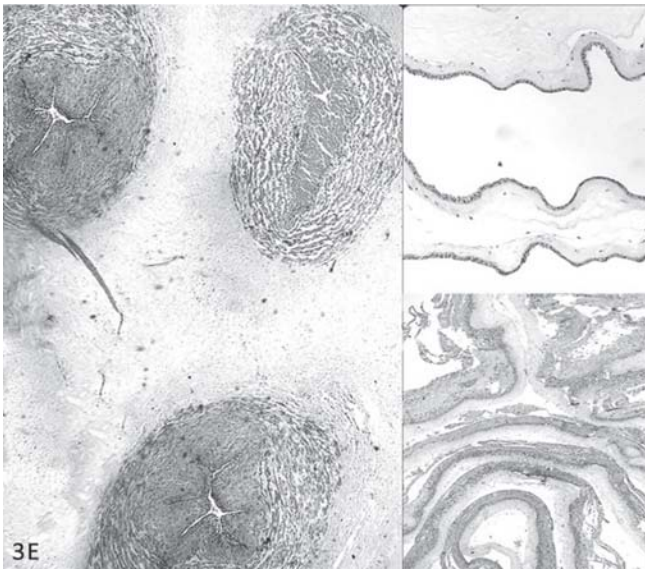


Figure 3E. Umbilical cord with two arteries and one vein, chorion, and amnion. (50x magnification)

Immunohistochemistry studies were done and showed differential positive expression for CK7 and negative CK20 expression which is consistent with the cytokeratin profile of breast carcinoma. Estrogen receptor determination was positive (ER+) with an intermediate nuclear expression in approximately 33% of tumor cells. GCDPF-15 and mammaglobin were also negative. TTF-1 was negative and an occult metastatic lung adenocarcinoma, which is also known to occur in pregnancy was ruled out. Comparison of the ER, PR, and HER2 receptor profile showed a positive ER and PR expression in both primary and metastatic lesions. HER2/neu expression was equivocal on immunohistochemistry and negative in HER2/neu dual in-situ hybridization in the primary tumor, with the placental metastasis also showing negative HER2/neu expression (Table 1A).

The patient was subsequently advised to undergo evaluation for tumor metastases because of the rapid progression of symptoms during her pregnancy, which she agreed to after the delivery. During this time, she already had back pain and dyspnea, and was under the care of the medical oncology service at the time this report was made. The pediatric service was also informed of the status of the placenta; evaluation of the newborn showed no clinical findings of malignancy. No imaging studies were done since there were no indications to do so.

Table 1. Comparison of the ER/PR and HER2 tumor antigen expression profile of the breast carcinoma and the placental metastasis.

Antigen	Tissue	
	Left breast core needle biopsy	Placental tissues with metastatic carcinoma
ER (IHC)	Positive	Positive
PR (IHC)	Positive	Positive
HER2/neu (IHC)	Equivocal	Negative
HER2/neu (DDISH)	Negative	----

IHC - immunohistochemistry

DDISH - dual-hapten in situ hybridization

Discussion

Defined as breast cancer within pregnancy, or one to two years after delivery, and more commonly known as "pregnancy-associated breast cancer" (PABC), this lesion presents as a palpable mass that has suffered delayed diagnosis due to confusion with pregnancy associated changes and is generally associated with an adverse prognosis for the mother with no established risks for the newborn.^{3,4} Pregnancy-associated cancer occurs in 89.6-172.6/100,000 maternities.⁵ In contrast, pregnancy-associated breast cancer occurs in 1 out of 3,000 maternities.⁶ Among all cases of pregnancy-associated cancer, 100 cases have been reported in scientific publication since 1951, and the most common of which is melanoma with 28 cases, with breast cancer coming in second at 16 cases. None of the 16 cases of breast cancer with placental metastasis documented fetal extension.⁷⁻⁹

Shochet expounded on how the placental extracellular matrix induces metastasis away from the placenta and directs metastasis to other organs thru modulating the ER α , TGF- β , Smad3/JNK phosphorylation, and integrin- α 5 expression.⁸ This is in correlation with the essential role of TGF- β in promoting the tumor growth and metastasis of breast cancer.¹⁰ It can be hypothesized that placental metastasis may be a failure of regulation of the crosstalk in the TGF- β , Smad3/JNK pathway to inhibit migration of tumor cells towards and into placental tissues.

Among documented cases, placental metastases have been noted in the intervillous stroma only.^{3,8,9} As to why there is no fetal extension of the tumor in

breast carcinoma among all 16 documented cases of placenta with metastatic carcinoma, when compared to metastatic melanoma which has the highest occurrence of placental metastasis and fetal extension with six of 28 cases having fetal extension, it is hypothesized that the difference in cell adhesion molecule and the probable lack of ability of $\alpha\beta 1$ integrin to induce tumor disruption of the materno-fetal vascular interface when compared to the ability of melanoma conferred hypothetically by the melanoma cell adhesion molecule MUC18 may explain the lack of fetal vessel metastasis.^{3,7,9} This may explain the lack of involvement of the fetus in breast carcinoma. This is in the setting of both tumors having VEGF involvement in angiogenesis, and the presence of MMP2 and MMP9 as matrix metalloproteinases common in both tumor types.^{10,11}

According to AJCC staging, having placental metastasis classifies this patient as Stage 4 which has 15% 5-year survival rate. But the expression of ER, mammaglobin, and GCDFP-15 also affects prognosis, possibly worsening the already dismal situation. Investigation regarding the ER expression and the lack of mammaglobin and GCDFP-15 led the authors to consider the role of the absence of expression. Although ER as a metastatic marker has a sensitivity of 75% and a specificity of 33%, while mammaglobin has a sensitivity of 76% and a specificity of 90%, and GCDFP-15 has a sensitivity of 74% and a specificity of 99%,^{12,13} Yang documented a decreased sensitivity for ER, mammaglobin, and GCDFP-15 in the metastasis when compared to the primary lesion.¹⁴

Luo and Eun Ha, and Nunez-Villar had described how a positive mammaglobin expression is associated with a more favorable prognosis.^{14,15} For this case particularly, a negative mammaglobin is associated with higher nuclear grade, and a higher risk of migration and invasion. Likewise, a negative GCDFP-15 is associated with a higher grade and an elevated Ki-67 index, indicating a less favorable prognosis.^{15,16}

A patient with an ER+/PR+ and HER2- receptor status has a median survival of 24.4 months after diagnosis of metastasis which is less than the survival of an ER+/PR+, and HER2+ patient of median 34.4 months.¹⁷ HER2/neu in-situ hybridization confirmatory testing was done to determine the HER2/neu status, given an initial equivocal IHC because of the impact of receptor discordance in prognosis.

When considering the impact to prognosis, ER discordance and loss as well as HER2 discordance

and loss are important factors in the prognosis of patients with metastatic breast carcinoma. Yu-Feng showed that as much as 20% of patients had converted to an ER negative metastatic carcinoma from a previously ER positive status, and as much as 38.1% of patients had converted to a PR negative metastatic carcinoma from a previously PR positive primary carcinoma. The HER2/neu loss in the metastasis when compared to the primary tumor confers statistically significant worse overall survival for the patient, with Yu-Feng showing statistically significant worse overall survival and post-recurrence survival if with HER2/neu receptor discordance. However, in such report, only 6.7% of cases showed HER2/neu receptor discordance, suggesting that a greater population of breast cancer cases will retain the original receptor status of the primary tumor.¹⁸ For this patient, there was no shift in receptor profile which may contribute to the prognosis, in relation to pregnancy and the stage of the breast carcinoma.

Compared to non-pregnant cases, Amant showed no difference in 5-year disease free survival and overall survival between pregnant and non-pregnant breast cancer cases although mortality rate appears to be doubled in the study of Johansson in 2011: the mortality rate among pregnant patients with breast cancer being 77/1,000 person per year, compared with mortality rate of 37.6/1,000 person per year among non-pregnant patients.^{19,20}

As such, all the information provided can aid in determining the prognosis and in the decision making for treatment. Unfortunately, long term adverse effects and prognosis of the baby, whether with placental metastasis or otherwise, have not yet been documented. In conclusion, pregnancy-associated breast cancer carries adverse prognosis for the mother. An issue causing problems for pregnant patients with breast cancer in those not presenting with placental metastasis is the inherent mechanism of the placenta to indirectly induce tumor metastasis to other organs by signaling the tumor away from the placenta. Such situation is commonly seen in other pregnancy-associated breast cancers with no placental metastasis. The pertinent problem in pregnancy-associated breast cancer with placental metastasis is the inability of the placenta to induce tumor metastasis away from itself.

Another concern in this lesion is that it carries yet unknown risk factors for newborns with no evidence of tumor extension. Given such situation,

the evaluation of the placenta for tumor metastasis is necessary to provide an insight on the possible impact of the malignancy to the newborn, such as invasion to the fetal vessels or proliferation into the maternal tissues such that infarction and thrombus may ensue. Likewise, the probable defect in the mechanisms inherent to the tumor and the placenta that allowed the tumor cells to invade the maternal side of the placenta may be important in future studies on pregnancy-associated breast cancer. This report provides additional information to the fund of knowledge regarding a very rare presentation of what is supposed to be a very common malignancy. Such information may, in the future, have tremendous impact, not only in the women who get them, but the offspring they carry.

Disclosures

This case report has no studies performed to animal or human participants. This case re-port includes only the specimen submitted by the patient for surgical histopathology evaluation to the section of anatomic pathology with consent for specimen evaluation and non-profit academic discussion or report. The authors of this case report have no conflict of interest in relation to the conduct of this case report and the publication thereof. This report did not receive funding from the institution nor from any service provider related to the processing of the histopathology specimen and the ancillary immunohistochemistry done. No funding was provided for the creation of this case report.

Acknowledgements

The authors would like to acknowledge the support of the faculty and staff of the Department of Pathology, College of Medicine, University of the East Ramon Magsaysay Memorial Medical Center, and the Section of Histopathology, Pathology Laboratory of the University of the East Ramon Magsaysay Memorial Medical Center. Dr. de los Reyes would like to acknowledge the assistance of Dr. Fe Abarcade los Reyes for her contribution in making this report possible.

References

1. Molckovsky A, Madarnas Y. Breast cancer in pregnancy: A literature review. *Breast Cancer Research and Treatment* 2007; 108(3): 333-8.
2. Shim M, Mok C, Chang K, et al. Clinical characteristics and outcome of cancer diagnosed during pregnancy. *Obstet Gynecol Sci* 2016; 59(1): 1.
3. Vetter G, Zimmermann F, Bruder E, Schulzke S, Hösli I, Vetter M. Aggressive breast cancer during pregnancy with a rare form of metastasis in the maternal placenta. *Geburtshilfe und Frauenheilkunde* 2014; 74(06): 579-82.
4. Navrozoglou I, Vrekoussis T, Kontostolis E, et al. Breast cancer during pregnancy: A mini-review. *Eur J Surg Oncol* 2008; 34(8): 837-43.
5. Lee Y, Roberts C, Young J, Dobbins T. Using hospital discharge data to identify incident pregnancy-associated cancers: a validation study. *BMC Pregnancy and Childbirth* 2013; 13(1).
6. Barnes D, Newman L. Pregnancy-associated breast cancer: A literature review. *Surg Clin North Am* 2007; 87(2): 417-30.
7. Hoellen F, Reibke R, Hornemann K, et al. Cancer in pregnancy. Part II: treatment options of breast and other non-gynecological malignancies. *Arch Gynecol Obstet* 2011; 284(6): 1481-94.
8. Epstein Shochet G, Drucker L, Pomeranz M, et al. First trimester human placenta prevents breast cancer cell attachment to the matrix: The role of extracellular matrix. *Molecular Carcinogenesis* 2016; 56(1): 62-74.
9. Ho C, Looi L. Maternal breast carcinoma metastases to the placenta: a case report and literature review. *Pathology* 2012; 44: S61.
10. Ben Brahimi E, Mrad K, Driss M, et al. Métastase placentaire d'un cancer du sein. *Gynécologie Obstétrique Fertilité* 2001; 29(7-8): 545-8.
11. Zigler M, Villares G, Dobroff A, et al. Expression of Id-1 Is Regulated by MCAM/MUC18: A missing link in melanoma progression. *Can Res* 2011; 71(10): 3494-504.
12. Dekker T, ter Borg S, Hooijer G, et al. Quality assessment of estrogen receptor and progesterone receptor testing in breast cancer using a tissue microarray-based approach. *Breast Cancer Research and Treatment* 2015; 152(2): 247-52.
13. Dabbs D. *Diagnostic Immunohistochemistry*. 4th ed. London: Elsevier Health Sciences; 2013; 763-98.
14. Yang M, Nonaka D. A study of immunohistochemical differential expression in pulmonary and mammary carcinomas. *Mod Pathol* 2010; 23(5): 654-61.
15. Núñez-Villar M, Martínez-Arribas F, Pollán M, et al. Elevated mamoglobin (h-MAM) expression in breast cancer is associated with clinical and biological features defining a less aggressive tumour phenotype. *Breast Cancer Research* 2003; 5(3).
16. Koh E, Cho Y, Mun Y, et al. Upregulation of human mamoglobin reduces migration and invasion of breast cancer cells. *Canc Invest* 2013; 32(1): 22-9.

17. Lobbezoo D, van Kampen R, Voogd A, et al. Prognosis of metastatic breast cancer subtypes: the hormone receptor/HER2-positive subtype is associated with the most favorable outcome. *Breast Cancer Research and Treatment* 2013; 141(3): 507-14.
18. Yang Y, Liao Y, Yang M, Peng N, Xie S, Xie Y. Discordances in ER, PR and HER2 receptors between primary and recurrent/metastatic lesions and their impact on survival in breast cancer patients. *Med Oncol* 2014; 31(10).
19. Amant F, von Minckwitz G, Han S, et al. Prognosis of women with primary breast cancer diagnosed during pregnancy: Results from an international collaborative study. *J Clin Oncol* 2013; 31(20): 2532-9.
20. Johansson A, Andersson T, Hsieh C, Cnattingius S, Lambe M. Increased mortality in women with breast cancer detected during pregnancy and different periods postpartum. *Cancer Epidemiology Biomarkers & Prevention* 2011; 20(9): 1865-72.