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Chasing Hippos: Implications of YAP1 and TAZ Expression in Pregnancy-associated Breast Cancer Tumorigenesis

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Abstract. *Background/Aim: The Hippo pathway is a molecular pathway recently associated with tumorigenesis, metastasis, and drug resistance. Pregnancy-associated breast cancer (PABC) is the most common malignancy diagnosed during gestation; however, the molecular mechanisms underlying PABC are largely unknown. The aim of the present study was to evaluate Hippo pathway transducers TAZ and YAP1 expression in PABC in relation to the clinicopathological characteristics of the disease. Patients and Methods: Formalin-fixed paraffin-embedded (FFPE) tissues from 21 PABC patients treated at Alexandra Hospital in Athens, Greece, were analyzed with immunohistochemistry. Results: Strong nuclear TAZ/YAP1 stanning was found in 48% of the PABC patients analyzed. Hormone receptor negative patients had a statistically significant correlation with strong positive expression of TAZ/YAP1 co-transcription factors. No association was observed with overall and disease-free survival. Conclusion: The Hippo pathway is de-regulated in a subset of PABC patients, highlighting the complex molecular background of the disease, which certainly requires further investigation.*

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The Hippo signaling pathway was firstly identified in genetic studies of *Drosophila melanogaster* and classified as a major suppressor of tissue overgrowth (1, 2). The Hippo pathway maintains tissue homeostasis and regulates cell proliferation and apoptosis by a well conserved kinase cascade, which cross-talks with several cellular signaling pathways (3, 4). The core component of the Hippo signaling mammalian Ste20-like kinase 1/2 (MST1/2) phosphorylates and thus activates large tumor suppressor 1/2 (LATS1/2), which further phosphorylates two transcriptional coactivators named yes-associated protein 1 (YAP1) and transcriptional coactivator with PDZ-binding motif (TAZ) that comprise the main effectors of the Hippo pathway. YAP1 and TAZ are normally retained in the cytoplasm through binding to 14-3-3 proteins and ubiquitination followed by proteasomal degradation is the final cellular destination (4, 5). Deregulation of the Hippo pathway includes translocation of the key transducers TAZ and YAP1 to the nucleus in combination with the transcriptional enhanced associated domain (TEAD) transcription factors 1-4, thus demonstrating significant oncogenic function (5, 6). Multiple theories have evolved regarding Hippo signaling de-regulation and crosstalk with several pathways (*e.g.*, Wnt/β-catenin, TGF-β, JNK) leading to carcinogenesis, metastasis, and drug resistance (7, 8). Additionally, the Hippo signaling pathway has been extensively explored in various tumors including metastatic breast cancer, triple-negative breast cancer (TNBC), and male breast cancer (7, 9, 10). To the best of our knowledge, this is the first study evaluating YAP1 and TAZ expression in pregnancy-associated breast cancer (PABC), a truly challenging situation with significantly increasing incidence rate.

PABC is generally defined as breast cancer diagnosed anytime during gestation, lactation, or within one year after delivery (11). Every year, 1 in 3,000-10,000 women is

diagnosed with PABC, which represents the most frequently diagnosed pregnancy-related malignancy (12). As women tend to defer childbearing to a later age, PABC incidence is expected to increase substantially in the upcoming years. Additionally, the application of non-invasive prenatal testing (NIPT) in all pregnant women, aiming to detect fetal abnormalities, has unquestionably increased the identification of asymptomatic PABC patients (13, 14). The genomic profile of PABC has recently been addressed in a systematic review, but the underlying mechanisms of the disease still require further investigation in order to explain PABC aggressiveness; advanced T stage in diagnosis, nodal involvement, high histologic grade, negative estrogen receptor (ER) and progesterone receptor (PR) status, and HER-2 over-expression (15, 16).

Toward this effort, the study of the Hippo pathway transducers TAZ and YAP1 in PABC aimed to further elucidate the oncogenic mechanism of PABC and to detect signal molecules that may serve as novel diagnostic biomarkers and therapeutic targets of anticancer drugs.

Patients and Methods

This cohort study of patients diagnosed with PABC was conducted at the Alexandra Hospital that is affiliated with the National and Kapodistrian University of Athens in Greece. All participants were required to sign the informed consent form according to the principles of the Declaration of Helsinki, to have completed the 18th year of age, and to have attended the Breast Unit of the Department of Obstetrics and Gynecology or the Department of Clinical Therapeutics at Alexandra Hospital in Athens, Greece. The study protocol was approved by the Institutional Review Board (IRB) of Alexandra Hospital (Protocol code: 908/15.11.2019; Date of approval: 15.11.2019).

Participants. By the time the written informed consent was granted, all medical records of women diagnosed with PABC in our Institution according to the inclusion criteria were retrospectively reviewed for the period 2000-2019. Additionally, all women diagnosed with the disease from January 2020 until December 2020 were also prospectively included in our study. The following clinicopathological data regarding PABC, and the patients' demographic characteristics were extracted from the medical files of each eligible patient; date of birth, gestational age at diagnosis, family cancer history, histopathologic evaluation (tumor size, stage, grade, lymph node status, hormone receptor and HER-2 expression), genetic testing, PABC treatment (*e.g.*, surgery, chemotherapy, immunotherapy, hormonotherapy, radiotherapy), and follow-up data. Furthermore, for each patient enrolled in the study, a sample of formalin-fixed paraffin-embedded (FFPE) tissue was obtained from the Department of Pathology in Alexandra Hospital to evaluate Hippo pathway transducers expression.

Immunohistochemistry. TAZ and YAP1 transducers expression in PABC was detected on FFPE tissue using the rabbit anti-YAP and anti-TAZ antibodies, clone D24E4 of the ImmPress REAGENT KIT, UNIVERSAL, Anti-mouse/rabbit Ig, VECTOR, at the dilution 1:50 and according to the manufacturer's protocol (Cell Signaling Technology, Danvers, MA, USA). Their expression was reported both in terms of percentage of tumor-expressing cells and staining intensity (0=absent, 1+=weak, 2+=moderate, 3+=strong). The topographic TAZ and YAP1 expression were evaluated in both the cytoplasm and the nucleus of tumor cells, and in the main cellular components, namely endothelial cells, non-lymphocytic stromal cells, and tumor-infiltrating lymphocytes (TILS) that were morphologically identified (9). Nuclear staining, which demonstrated variable expression, was further classified as negative/weak positive or strong positive following the study by Rodríguez-Núñez *et al*.; tissue was given a score which resulted from multiplying the nuclear staining intensity from 0 (no staining) to 3 (strong staining) by the extension based on the percentage of positive cells (from 0-3). Thus, samples were grouped as negative or weak positive (scores 0-2), and strong positive (scores 3-9) (17).

Statistical analysis. Descriptive statistics were used to summarize study participants' characteristics. The Pearson's Chi-Squared and Fisher Exact Tests, when appropriate, for categorical variables were used to investigate the correlation among the immunohistochemical YAP1/TAZ expression and the clinicopathological characteristics. Survival curves were estimated with the Kaplan-Meier method. All the statistical analyses were performed using the SPSS v24 (IBM, Armonk, NY, USA, SPSS Statistics) software. p-value<0.05 was considered statistically significant.

Results

Patient characteristics. Overall, 21 women diagnosed with PABC were enrolled in this study and screened for the expression of the Hippo signaling transducers TAZ and YAP1. Detailed data regarding the demographic variables and pregnancy characteristics of the patients including age, gestational age at diagnosis, ethnicity, and family cancer history are demonstrated in Table I. The age at diagnosis ranged from 28 to 42 years, with a mean age of 35.1 years (SD=3.83; range=28.0-42.0). Six patients (38%) were diagnosed with PABC within the first year after delivery, whereas 10 patients (63%) were diagnosed during pregnancy. Most of the participants reported a negative family cancer history (76%), whereas only 5 patients (24%) had a positive family history of lung, prostate, breast, or colorectal cancer among first degree relatives.

No association was observed between YAP1/TAZ nuclear expression, the gestational age at diagnosis, and the family cancer history.

Histopathological characteristics. The histopathological features of the 21 PABC patients examined in this study are summarized in Table II. The most frequently diagnosed histopathological type was invasive ductal carcinoma (IDC) (81%), whereas a few cases of invasive lobular (ILC) and metaplastic carcinoma were also identified. The vast majority of tumors were of high grade (81%) and the mean value of tumor size was 4.21 cm (SD=3.01; range=0.8-12.0

Table I. *Patient characteristics*.

Age (y) at diagnosis		
Mean±SD		35.05±3.39
Median (min-max)		36.00 (28-42)
Gestational age at diagnosis	N	N (%)
1st trimester	1	6%
2nd trimester	2	13%
3rd trimester	7	44%
Postpartum	6	38%
N/A	5	24%
Ethnicity		
Greek	18	86%
Non-Greek	3	14%
Family cancer history		
Positive	5	24%
Negative	16	76%

Table II. *Histopathological characteristics*.

Characteristics		N (%)
Histopathological type	Invasive ductal carcinoma (IDC)	81
	Invasive lobular carcinoma (ILC)	9.5
	Metaplastic carcinoma	9.5
Tumor grade	Grade II	19
	Grade III	81
Tumor size	4.21 cm (0.8-12)	
Hormone receptor (HR) status	Positive	60
	Negative	40
Estrogen receptor (ER) status	Positive	50
	Negative	50
Progesterone receptor (PR) status	Positive	50
	Negative	50
HER-2	Positive	45
	Negative	55
Ki-67	>20%	75
	<20%	25
Stage	I	14.3
	II	52.3
	III	23.9
	IV	9.5
Molecular subtypes	Luminal A	14.3
	Luminal B/HER-2 positive	28.6
	Luminal B/HER-2 negative	14.3
	TNBC	23.8
	HER-2 positive	14.3
	N/A	4.8

cm). In most cases analyzed, high levels of Ki-67 >20% were detected (75%). Only two women (10%) were diagnosed with primary metastatic PABC. Nineteen patients received adjuvant chemotherapy (90%). The majority had a diagnosis of stage II disease (52.4%).

The nuclear YAP1/TAZ staining was classified as negative/weak positive in 52% (11/21) and as strong positive in 48% (10/21) of the patients analyzed. As far as the expression of hormone receptors (HRs) is concerned, HR negative status was associated with strong nuclear expression of the Hippo pathway transducers TAZ and YAP1 in tumor cells (p-value=0.006). Furthermore, when evaluating separately the ER and the PR expression, a statistically significant correlation was identified solely among the PR negative status and the strong positive nuclear YAP1/TAZ expression (p-value=0.007). Representative patterns of TAZ and YAP1 immunohistochemical staining are illustrated in Figure 1. No significant association was observed with the histopathological type, tumor grade and size, HER-2 and Ki-67 expression, molecular subtype (Luminal A, Luminal B - HER-2 positive/negative, TNBC, HER-2 positive) and stage of the disease.

YAP1/TAZ nuclear expression and prognosis. We next investigated the impact of TAZ and YAP1 expression on the overall survival (OS) and disease-free survival (DFS) rate of PABC patients. Follow-up data were retrieved from the medical files of 15 out of 21 PABC patients enrolled in this study; 2 deaths were recorded, and the remaining 13 patients demonstrated a mean OS rate of 172.348 months (Figure 2A, 95%CI=134.305-210.392). Furthermore, as far as progression-free disease is concerned, the following events were reported; local breast relapse was observed in four patients, liver and bone metastases developed in three patients, lung metastasis in two, and brain metastasis in a single patient. In total, 6 patients were characterized as metastatic; 2 primary metastatic PABC patients, one of which showed further signs of relapse with bone and lung metastases 5 months after the initial diagnosis, and 4 secondary metastatic patients. The progression-free survival (PFS) rate was not estimated as the cohort was too small to draw any conclusions. Additionally, the mean DFS rate was estimated to be 86.453 months (Figure 2B, 95%CI=54.283-118.622). Even though most patients characterized by strong positive nuclear YAP1/TAZ staining relapsed or passed away, no statistically significant correlation was identified with the OS and DFS rates.

Discussion

PABC is the most common malignancy accompanying pregnancy (16). The distinct clinical and genetic data of PABC are not fully elucidated (15). Herein, we have conducted a translational study of Hippo pathway transducers in relation to the clinicopathological characteristics of PABC.

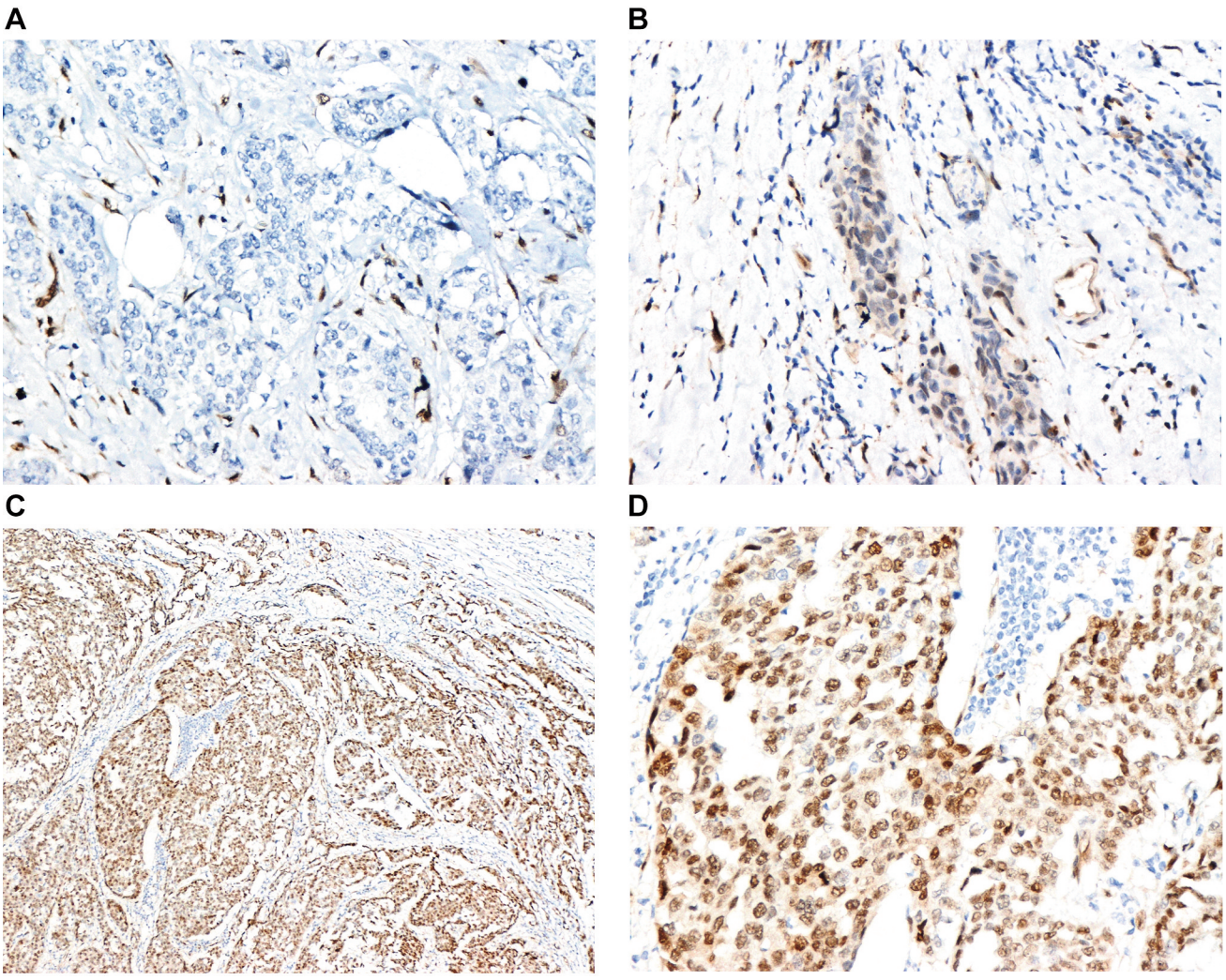

Figure 1. *TAZ and YAP1 immunohistochemical staining. A) No nuclear staining of the neoplastic cells (´200). B) Weak nuclear staining of some neoplastic cells (´200). C) YAP1/TAZ strong nuclear staining of the neoplastic cells (´50). D) YAP1/TAZ strong nuclear staining of the neoplastic cells (´200).*

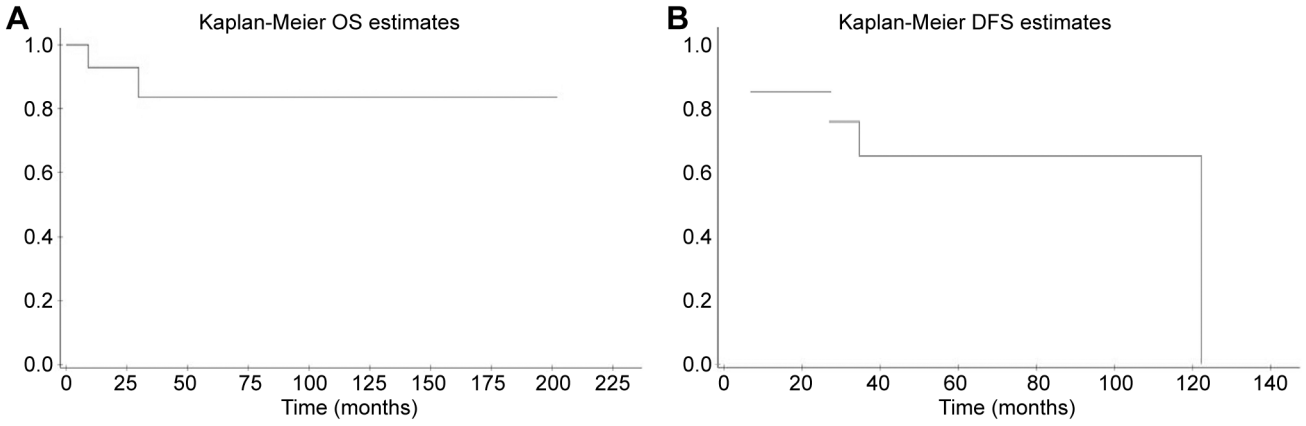

Figure 2. *Kaplan-Meier curves of overall survival (A) and disease-free survival (B).*

The Hippo pathway was found to be de-regulated in 10/21 cases (48%), implying that almost half of PABC patients may present with this abnormality. When we further studied the correlation between HR status and Hippo pathway activity, we observed a statistically significant result for HR negative patients and YAP1/TAZ strong nuclear positivity (p=0.006). This result was also prominent for PR negative cases (p=0.007). These findings are in accordance with previous publications showing that PABC are commonly tumors with low HR status (16, 18). Additionally, our data confer a possibly crucial molecular mechanism for the development of a subset of PABC cases, which are generally shown to have a complex genetic and molecular background (8, 15).

When we tested the histopathological type, tumor grade and size, HER-2 status and Ki-67 expression, molecular subtype, and stage of the disease, we did not find any statistically significant results. Possibly, these findings depict the molecular complexity of the disease (15, 19-21). Hippo signaling seems not to be present and meaningfully active in all PABC cases. Furthermore, Hippo signaling positivity did not have a statistically significant correlation with the gestational age at diagnosis of PABC during or after pregnancy. Here, it should be highlighted that our data show a higher percentage of patients being diagnosed during pregnancy than postpartum, as is published by others (16).

Our study did not reveal any correlations between OS, DFS, and Hippo pathway. Even though most patients with Hippo pathway de-regulation experienced relapse or died from the disease, no statistically significant correlations were found. However, a longer follow up may be needed to extract more accurate conclusions regarding these clinical parameters.

The characteristics of our study population are representative of PABC patients (16, 18). The majority harbor an aggressive disease with high Ki-67 levels, low HR status, and grade 3 tumors. Only 2 (9.5%) patients were primarily metastatic, 4 developed metastases at a later course of their disease, while 4 patients experienced local relapse. Stage II and III patients were the majority, in agreement with previous publications. Furthermore, luminal B and TNBC patients were most commonly found in our cohort, also in accordance with previous publications (16).

The present study had several limitations that need to be addressed. Meaningful information was not reported in 6 cases, thus decreasing the number of our patients with clinical data to 15 included cases and as a result, the statistical power was limited and anticipated associations were not observed. Even though our study is limited by the retrospective nature of the analysis and its small number of patients, it adds an important amount of clinical data regarding the clinical characteristics and outcome of PABC, as well as the significance of the Hippo pathway in the development of this rare disease.

Conclusion

To conclude, Hippo pathway signaling is de-regulated in a subset of PABC patients. We are the first to report that almost half of PABC patients had strong nuclear immune-positivity for YAP1/TAZ co-transcription factors, implying high activity and de-regulation of the Hippo pathway. HR negative tumors were associated with the Hippo pathway, depicting an important role of this molecular signaling in the development of these PABC tumors. PABC remains a rare tumor entity with distinct clinical and molecular characteristics, with the Hippo pathway playing a significant role in the molecular complexity of these tumors.

Conflicts of Interest

The Authors declare the following financial interests/personal relationships, which may be considered as potential competing interests: FZ has received honoraria for lectures and served in an advisory role for Astra-Zeneca, Daiichi, Eli-Lilly, Merck, Novartis, Pfizer, and Roche. MAD has received honoraria from participation in advisory boards from Amgen, Bristol-Myers-Squibb, Celgene, Janssen, Takeda. The remaining Authors (AK, AMK, MAP, KA, AN, EZ, GB, DT) declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

Authors' Contributions

Conceptualization, Anastasios Kyriazoglou, Meletios-Athanasios Dimopoulos and Flora Zagouri; Data curation, Anna-Maria Korakiti, Alkistis-Maria Papatheodoridi, Eleni Zografos, Garyfalia Bletsa and Dimitris Tsakogiannis; Funding acquisition, Anastasios Kyriazoglou, Meletios-Athanasios Dimopoulos and Flora Zagouri; Methodology, Alkistis-Maria Papatheodoridi, Kleoniki Apostolidou and Afroditi Nonni; Supervision, Meletios-Athanasios Dimopoulos and Flora Zagouri; Validation, Anastasios Kyriazoglou, Anna-Maria Korakiti and Flora Zagouri; Writing – original draft, Anastasios Kyriazoglou and Anna-Maria Korakiti; Writing – review & editing, Anastasios Kyriazoglou, Anna-Maria Korakiti, Alkistis-Maria Papatheodoridi, Kleoniki Apostolidou, Afroditi Nonni, Eleni Zografos, Garyfalia Bletsa, Dimitris Tsakogiannis, Meletios-Athanasios Dimopoulos and Flora Zagouri.

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References

1 Jia J, Zhang W, Wang B, Trinko R and Jiang J: The Drosophila Ste20 family kinase dMST functions as a tumor suppressor by restricting cell proliferation and promoting apoptosis. Genes Dev *17(20)*: 2514-2519, 2003. PMID: 14561774. DOI: 10.1101/gad.1134003

2 Pantalacci S, Tapon N and Léopold P: The Salvador partner Hippo promotes apoptosis and cell-cycle exit in Drosophila. Nat Cell Biol *5(10)*: 921-927, 2003. PMID: 14502295. DOI: 10.1038/ncb1051

3 Meng Z, Moroishi T and Guan KL: Mechanisms of Hippo pathway regulation. Genes Dev *30(1)*: 1-17, 2016. PMID: 26728553. DOI: 10.1101/gad.274027.115

4 Varelas X: The Hippo pathway effectors TAZ and YAP in development, homeostasis and disease. Development *141(8)*: 1614-1626, 2014. PMID: 24715453. DOI: 10.1242/dev.102376

5 Moroishi T, Hansen CG and Guan KL: The emerging roles of YAP and TAZ in cancer. Nat Rev Cancer *15(2)*: 73-79, 2015. PMID: 25592648. DOI: 10.1038/nrc3876

6 Ehmer U and Sage J: Control of proliferation and cancer growth by the Hippo signaling pathway. Mol Cancer Res *14(2)*: 127-140, 2016. PMID: 26432795. DOI: 10.1158/1541-7786.MCR-15-0305

7 Wei C, Wang Y and Li X: The role of Hippo signal pathway in breast cancer metastasis. Onco Targets Ther *11*: 2185-2193, 2018. PMID: 29713187. DOI: 10.2147/OTT.S157058

8 Kyriazoglou A, Liontos M, Zakopoulou R, Kaparelou M, Tsiara A, Papatheodoridi AM, Georgakopoulou R and Zagouri F: The role of the Hippo pathway in breast cancer carcinogenesis, prognosis, and treatment: a systematic review. Breast Care (Basel) *16(1)*: 6-15, 2021. PMID: 33716627. DOI: 10.1159/000507538

9 Vici P, Ercolani C, Di Benedetto A, Pizzuti L, Di Lauro L, Sperati F, Terrenato I, Gamucci T, Natoli C, Di Filippo F, Botti C, Barba M, Mottolese M, De Maria R and Maugeri-Saccà M: Topographic expression of the Hippo transducers TAZ and YAP in triple-negative breast cancer treated with neoadjuvant chemotherapy. J Exp Clin Cancer Res *35*: 62, 2016. PMID: 27039292. DOI: 10.1186/s13046-016-0338-7

10 Di Benedetto A, Mottolese M, Sperati F, Ercolani C, Di Lauro L, Pizzuti L, Vici P, Terrenato I, Sperduti I, Shaaban AM, Sundara-Rajan S, Barba M, Speirs V, De Maria R and Maugeri-Saccà M: The Hippo transducers TAZ/YAP and their target CTGF in male breast cancer. Oncotarget *7(28)*: 43188-43198, 2016. PMID: 27248471. DOI: 10.18632/oncotarget.9668

11 Lee GE, Mayer EL and Partridge A: Prognosis of pregnancy-associated breast cancer. Breast Cancer Res Treat *163(3)*: 417-421, 2017. PMID: 28365832. DOI: 10.1007/s10549-017-4224-6

12 de Haan J, Verheecke M, Van Calsteren K, Van Calster B, Shmakov RG, Mhallem Gziri M, Halaska MJ, Fruscio R, Lok CAR, Boere IA, Zola P, Ottevanger PB, de Groot CJM, Peccatori FA, Dahl Steffensen K, Cardonick EH, Polushkina E, Rob L, Ceppi L, Sukhikh GT, Han SN, Amant F and International Network on Cancer and Infertility Pregnancy (INCIP): Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. Lancet Oncol *19(3)*: 337-346, 2018. PMID: 29395867. DOI: 10.1016/S1470-2045(18)30059-7

13 Amant F, Verheecke M, Wlodarska I, Dehaspe L, Brady P, Brison N, Van Den Bogaert K, Dierickx D, Vandecaveye V, Tousseyn T, Moerman P, Vanderstichele A, Vergote I, Neven P, Berteloot P, Putseys K, Danneels L, Vandenberghe P, Legius E and Vermeesch JR: Presymptomatic identification of cancers in pregnant women during noninvasive prenatal testing. JAMA Oncol *1(6)*: 814-819, 2015. PMID: 26355862. DOI: 10.1001/jamaoncol.2015.1883

14 Lenaerts L, Jatsenko T, Amant F and Robert Vermeesch J: Noninvasive prenatal testing and detection of occult maternal malignancies. Clin Chem *65(12)*: 1484-1486, 2019. PMID: 31604758. DOI: 10.1373/clinchem.2019.306548

15 Korakiti AM, Moutafi M, Zografos E, Dimopoulos MA and Zagouri F: The genomic profile of pregnancy-associated breast cancer: a systematic review. Front Oncol *10*: 1773, 2020. PMID: 33014874. DOI: 10.3389/fonc.2020.01773

16 Wang B, Yang Y, Jiang Z, Zhao J, Mao Y, Liu J and Zhang J: Clinicopathological characteristics, diagnosis, and prognosis of pregnancy-associated breast cancer. Thorac Cancer *10(5)*: 1060-1068, 2019. PMID: 30920126. DOI: 10.1111/1759-7714.13045

17 Rodríguez-Núñez P, Romero-Pérez L, Amaral AT, Puerto-Camacho P, Jordán C, Marcilla D, Grünewald TG, Alonso J, de Alava E and Díaz-Martín J: Hippo pathway effectors YAP1/TAZ induce an EWS-FLI1-opposing gene signature and associate with disease progression in Ewing sarcoma. J Pathol *250(4)*: 374-386, 2020. PMID: 31880317. DOI: 10.1002/path.5379

18 Reed W, Sandstad B, Holm R and Nesland JM: The prognostic impact of hormone receptors and c-erbB-2 in pregnancy-associated breast cancer and their correlation with BRCA1 and cell cycle modulators. Int J Surg Pathol *11(2)*: 65-74, 2003. PMID: 12754622. DOI: 10.1177/106689690301100201

19 Lehn S, Tobin NP, Sims AH, Stål O, Jirström K, Axelson H and Landberg G: Decreased expression of Yes-associated protein is associated with outcome in the luminal A breast cancer subgroup and with an impaired tamoxifen response. BMC Cancer *14*: 119, 2014. PMID: 24559095. DOI: 10.1186/1471-2407-14-119

20 Maugeri-Saccà M, Barba M, Pizzuti L, Vici P, Di Lauro L, Dattilo R, Vitale I, Bartucci M, Mottolese M and De Maria R: The Hippo transducers TAZ and YAP in breast cancer: oncogenic activities and clinical implications. Expert Rev Mol Med *17*: e14, 2015. PMID: 26136233. DOI: 10.1017/erm.2015.12

21 Díaz-Martín J, López-García MÁ, Romero-Pérez L, Atienza-Amores MR, Pecero ML, Castilla MÁ, Biscuola M, Santón A and Palacios J: Nuclear TAZ expression associates with the triple-negative phenotype in breast cancer. Endocr Relat Cancer *22(3)*: 443-454, 2015. PMID: 25870251. DOI: 10.1530/ERC-14-0456

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