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Gene expression in luminal A breast cancer and its correlation with chemoradiotherapy outcome and recurrence

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ABSTRACT

Background*:** Breast cancer is a common cancer that affects women. The Luminal A subtype of breast cancer is defined by low Ki67 expression (<14%), Her-2 negative, and positive ER and PR. Luminal A exhibits a favorable prognosis compared to other breast cancer types. ***Materials and Methods: Gene expression profiling was employed in this investigation to discover genes linked to clinical efficacy and recurrence in Luminal A breast cancer tissue samples. The study's overarching goal was to discover new therapeutic targets by deciphering the molecular mechanisms behind Luminal A breast cancer. ***Results:*** Our analysis revealed specific genes linked to Luminal A breast cancer, and their expression levels were correlated with clinical outcomes. High expression of certain genes was associated with improved clinical efficacy and a reduced recurrence rate. ***Conclusion:*** The study provides valuable insights into the molecular mechanisms of Luminal A breast cancer, offering potential targets for personalized therapeutic approaches.

INTRODUCTION

One of the most prevalent cancers in women, breast cancer is also one of the most rapidly growing cancer types in the country [1, 2]. Every year, millions of people get the devastating news that they have breast cancer, making it one of the most frequent malignancies in the world [3, 4]. Between 2015 and 2018, a grand total of 20.15 million women were diagnosed with breast cancer globally, as per the data. Out of the 20.2 million women diagnosed with breast cancer globally in 2020, around 23,000 lost their lives to the disease [5-7]. Breast cancer occurs in almost every country in the world, and can affect any woman after puberty, and its prevalence increases with age [8, 9]. The prognosis for a woman with breast cancer is better if the disease is detected and treated early. Breast cancer can be categorized into various subtypes based on molecular markers, including Luminal A, Luminal B, HER 2 positive, and triple negative [10, 11]. The purpose of this study was to examine gene expression in type LuminalA breast cancer and see whether there is an association with clinical efficacy and recurrence [12, 13]. This subtype of breast cancer is associated with a better prognosis and a reduced recurrence rate. We first aimed to clarify the specific expression of genes in the pathological process of Luminal A breast cancer, including gene expression data, efficacy feedback, and recurrence during the Luminal A breast cancer follow -up. In order to find potential correlations, we examined the data in the GEO (Gene Expression Monibus) and TCGA (The Cancer Genome Atlas) databases, created patient gene expression profiles, and compared the results with survival analysis, GO (Gene Ontology) analysis, and other findings [14–16].

Bright Human epidermal growth factor receptor-2 (Her-2) negativity, low Ki67 expression (<14%), and positive for the estrogen and progesterone receptors are characteristics of breast cancer. It has a better prognosis than other subtypes. Although the cure rate for Luminal A breast cancer is relatively high, however, some patients still face challenges with variable response to treatment and risk of recurrence. In contemporary clinical practice, we understand that a thorough investigation of the gene expression features of patients with Luminal A breast cancer may enable us to more precisely categorize patient subgroups and offer a more dependable foundation for individualized treatment. In light of this finding, the current study set out to investigate the link between gene expression, clinical consequences, and recurrence in Luminal A breast cancer patients in order to identify novel diagnostic markers that could enhance the accuracy of diagnosis and treatment for this subtype. Accuracy of response prediction.

The literature review indicates that type Luminal A breast cancer is associated with high expression levels of XBP 1 (X-box binding protein 1), GATA 3 (GATA binding protein 3), FOXA 1 (Forkhead Box A1), TFF 3 (Trefoil Factor 3), ESR 1 (Estrogen

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Receptor 1), SCUBE2 (Signal Peptide-CUB-EGF-Like Domain-Containing Protein 2), TREFOIL, and FACTOR3 gene [17, 18]. Significant correlations have been found between the degree of expression and efficacy, recurrence, and other conditions. Of greater interest, a portion of these genes do not show the same expression range in other breast cancer types, which means that we may have found specific markers for type Luminal A breast cancer. The aforementioned genes' expression was subjected to a survival analysis, and genes with substantial survival importance were found [19, 20]. Hereditary breast cancer is strongly linked to the BRCA 1 and BRCA 2 genes. The proteins they encode play important functions in cells such as DNA repair and cell cycle regulation. Mutations in the BRCA 1 and BRCA 2 genes can lead to impaired DNA repair mechanisms, increasing the risk of breast cancer [21, 22]. Certain clinical characteristics are frequently observed in breast cancer patients who carry BRCA 1 and BRCA 2 mutations. Some of the symptoms that may indicate a BRCA 1 or BRCA 2 mutation include a strong family history of the disease, breast cancer in both breasts, breast cancer in men, and an abnormally high rate of ovarian cancer [23, 24].

Moreover, we found that these genes may be related to certain signaling pathways, and found that they regulate cellular amide metabolism process, nucleotide-glucose metabolism process, nucleotide-glucose metabolism process and other pathways, implying that they may directly or indirectly affect the efficacy and recurrence of type Luminal A breast cancer. This provides clues for the clinical selection of more targeted treatment strategies, as well as the possible further development of targeted therapies [25, 26]. In light of this, we are performing additional experimental validation to investigate the precise function of these genes and signaling pathways in the development of Luminal A breast cancer [27]. We expect that in the future, it can provide more specific clinical guidance, enabling efficacy prediction and recurrence prevention in the treatment of type Luminal A breast cancer. Overall, our study makes an important contribution to understanding gene expression in type Luminal A breast cancer and its relevance to clinical efficacy and recurrence.

By diving into the complex terrain of gene expression in Luminal A breast cancer, this groundbreaking study offers a new viewpoint to the field of scientific inquiry. The unique contribution lies in our focused pursuit of unraveling the specific genes associated with Luminal A subtype and their direct correlation with clinical efficacy and recurrence. By addressing this crucial gap in current understanding, we aim to unearth novel diagnostic markers that have the potential to revolutionize the precision of diagnosis and treatment response prediction for Luminal A breast cancer patients. This study, with its emphasis on the molecular intricacies of Luminal A breast cancer, endeavors to pave the way for a paradigm shift towards personalized and more effective therapeutic strategies, marking a significant step forward in the field of breast cancer research.

MATERIALS AND METHODS

Luminal A breast cancer gene expression studies often employ publically available gene expression datasets collected from the whole-genome expression databases GEO and TCGA to examine relationships between gene expression and clinical effectiveness, recurrence, and other outcomes.

Data collection: We first searched and downloaded the gene expression dataset for type Luminal A breast cancer from the GEO and TCGA databases. For the GEO database, searches were performed using the keywords "breast cancer", "gene expression profile" and "Luminal A". For the TCGA database, we screened out the samples with the Luminal A types in breast cancer.

Data preprocessing: the preprocessing of the downloaded gene expression data. Including the filtering of non-expressed genes, the quality control of samples and genes, data standardization and other steps. The purpose of this step is to ensure comparability of data and reduce technical bias.

Differential expression analysis: Differential expression analysis of the preprocessed data using the limma package in R language. The most significantly differentially expressed genes were found by calculating the expression of each gene between Luminal A and normal samples.

Survival analysis: Survival analysis of differentially expressed genes using clinical data from the TCGA database. To examine the correlation between gene expression and patient survival, the Survival and Survminer packages in R were utilized. The analyses included Kaplan-Meier survival analysis and the Cox proportional hazards model.

Functional enrichment analysis: The functional enrichment analysis was carried out using tools such as DAVID (Database for Annotation, Visualization, and Integrated Discovery) [28] and Gene Set Enrichment Analysis (GSEA) [29], among others, to identify the biological processes and signaling pathways associated with the differentially expressed genes.

Statistics and data visualization: All statistical analyses and hypothesis testing are performed in the R language. Data visualization was assisted with ggplot2, pheatmap and other related R packages.

RESULT

Through gene expression profiling, we further screened a number of genes positively associated

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with ERBB 2 gene in type Luminal A breast cancer, including PGAP 3, GRB 7 and STARD3 *et al.* There is a tight association between high expression of these genes and overexpression of ERBB 2(figure 1).

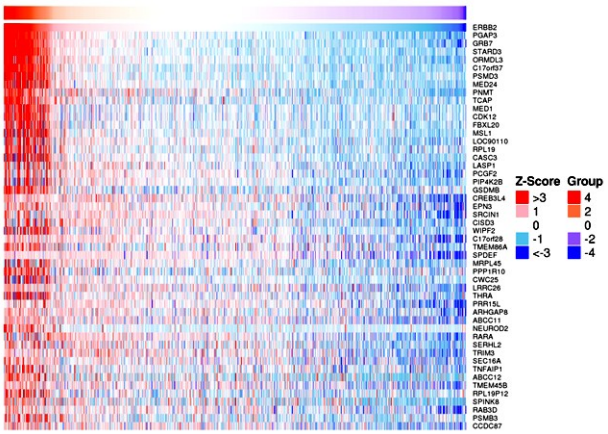

Figure 1. A positive correlation of gene expression associated with ERBB 2 in breast cancer. The right vertical axis shows the gene name, and red indicates a positive correlation in this case study of ERBB 2 gene expression in breast cancer. Blue indicates a negative correlation.

Survival analysis results

According to the above clinical data, the upper and lower tertiles of gene expression profiles were recorded as high and low expression, and high expression of the following genes GATA 3, XBP 1, FOXA 1, TFF 3, ESR 1, SCUBE2 was associated with better survival and low recurrence rate, (figure 2).

According to the gene expression in breast cancer, we made GO pathway analysis, and found that pathways such as regulating cellular amide metabolism, nucleotide-sugar metabolism, and nucleotide-sugar metabolism played a key regulatory role (FDR <0.05) (figure 4).

The GO analysis results of related pathways in breast cancer show that the blue part represents the result of FDR<0.05, involving the regulation of cellular amide metabolism, nucleotide sugar metabolism and other pathways. These pathways are significant in the development and occurrence of breast cancer, as shown by the statistical significance of these data.

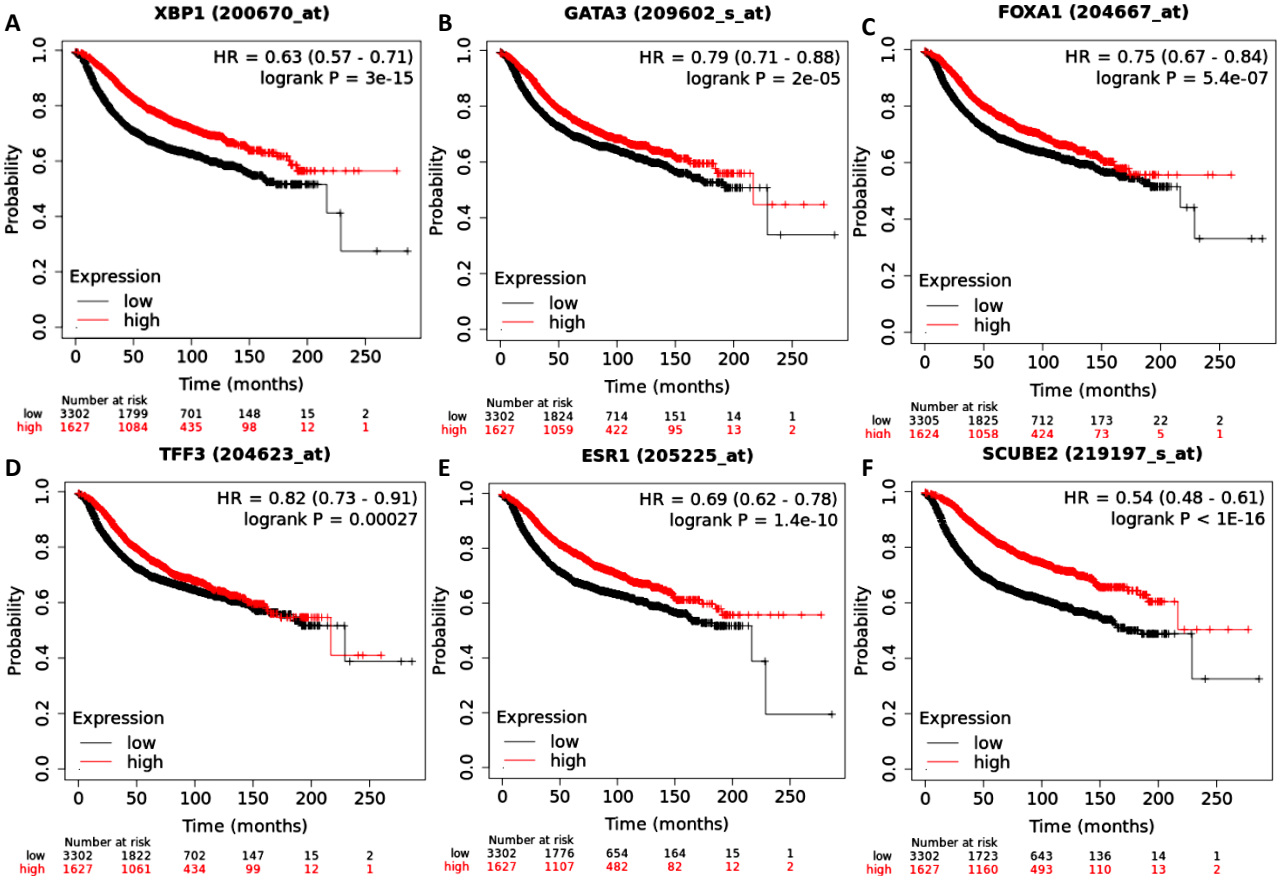

Figure 2. Genetic markers for breast cancer prognosis **A** higher death rate is associated with high XBP1 expression in breast cancer patients; **B** a higher death rate is associated with high GATA3 expression in breast cancer patients; **C:** The mortality rate is higher for breast cancer patients who express a high level of FOXA1. A greater death rate is observed in breast cancer patients with high expression of TFF3. **E:** The death rate for breast cancer patients is increased when ESR1 expression is high; A greater mortality rate is observed in breast cancer patients with high expression of SCUBE2. A statistically significant result is defined as P<0.05.

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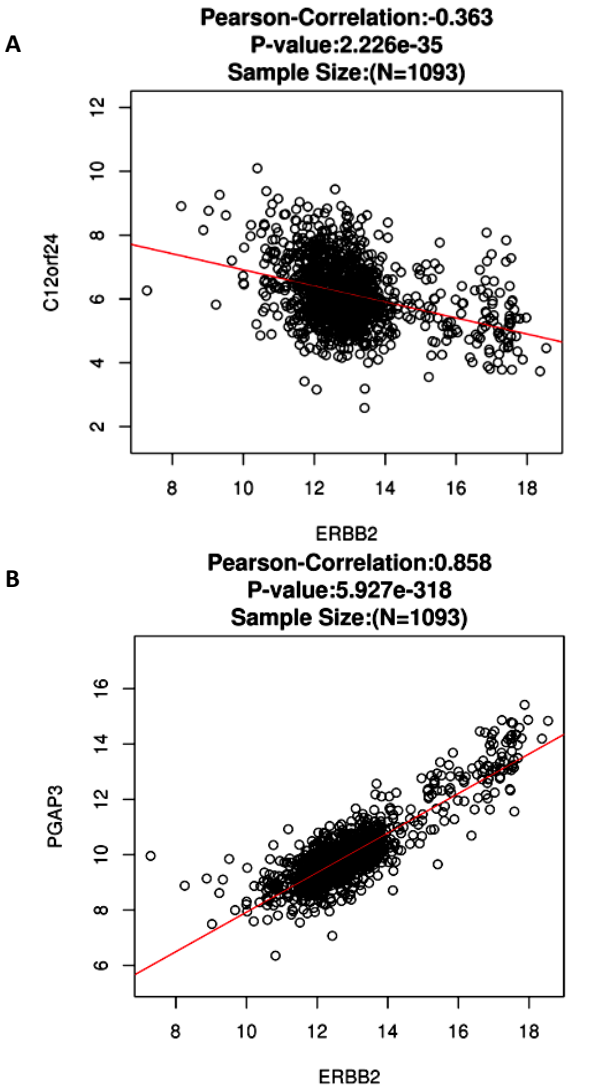

Figure 3. Gene with the strongest association with ERBB 2; **A:** C12orf14, Pearson coefficient of-0.363, negative correlation,; **B:** PGAP 3, Pearson coefficient of 0.858, positive correlation. All the P-values were statistically significant.

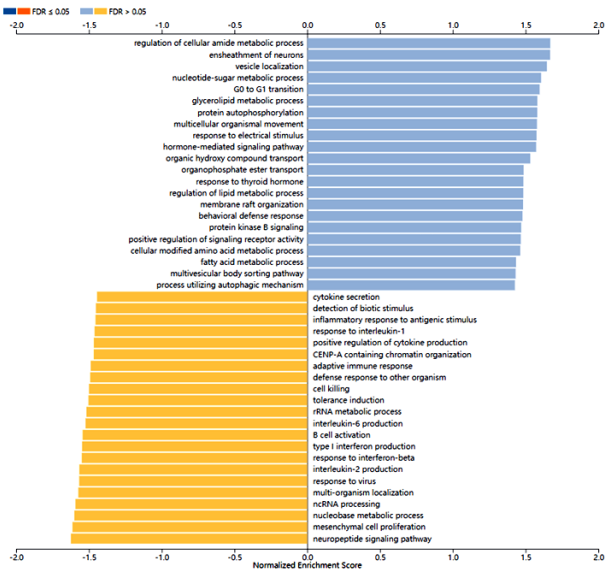

Figure 4. GO analysis of related pathways in breast cancer.

DISCUSSION

In this study, gene expression profiling of patients with type Luminal A breast cancer identified some genes associated with this subtype and further investigated the role of these genes in clinical efficacy and recurrence. The results suggest that high expression of certain genes is associated with better clinical efficacy and low recurrence rate. Insights into the molecular processes and personalized treatment of type LuminalA breast cancer can be provided by these new targets.

Our interest has been piqued by the positive link between the PGAP 3 and ERBB 2 genes, which is shown in type Luminal A breast cancer. PGAP 3 is a phosphoglyceride lipoinositase involved in the regulation of the phosphatidylinositol signaling pathway. Its high expression may be related to the activation of ERBB 2 signaling pathway, thus promoting tumor proliferation and metastasis[29]. Secondly, high expression of the GRB 7 gene was also associated with overexpression of ERBB 2. GRB 7 encodes a signal transduction molecule involved in the regulation of multiple cellular growth factor receptor signaling pathways. High expressed GRB 7 may enhance the activity of ERBB 2 signaling through its interaction with ERBB 2, thereby promoting tumor growth and metastasis [30]. Finally, high expression of the STARD3 gene was also associated with overexpression of ERBB 2. An integral part of carcinogenesis and development, STARD3 is also involved in the transport and metabolism of cholesterol. The activation of the ERBB 2 signaling pathway, which impacts tumor proliferation and metastatic capacity, may be associated with its high expression [31].

The pathway regulating the metabolism of cytosamide is of great significance in breast cancer. Cytoamides are a class of bioactive molecules, including fatty acids, glycerophosphate, etc. Vital cellular functions like energy consumption, cell signaling, and biofilm structure maintenance rely on these chemicals. Abnormal control of cytosamide metabolism may have a close relationship to the development and occurrence of breast cancer since the metastasis and proliferation of breast cancer cells require a substantial quantity of energy supply and the support of cell signal transduction. Additionally, the nucleotide glucose metabolism pathway is a key player in breast cancer cases. A wide variety of essential biological activities rely on nucleotides, including cell signaling, DNA and RNA production, and other cellular components. There is a tight relationship between sugar metabolism, cell proliferation, and metastasis; both pathways are critical for cellular energy supply. The disruption of DNA damage repair and cell cycle regulation, which in turn promotes tumor development, can be brought about by abnormalities in nucleotide glucose

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metabolism in breast cancer.

Finding out which molecular mechanisms and important biological processes contribute to the development of breast cancer is the main reason why these GO pathway analysis results are important. Further research into these pathways will shed light on the pathophysiology of breast cancer and lead to the development of novel diagnostic and therapeutic targets. To provide further context for the aforementioned processes, breast cancer cells may develop an energy metabolism imbalance, which in turn impacts cell proliferation and metastasis, if the regulation of cytosamide metabolism is disrupted. Abnormalities in the nucleotide sugar metabolism process may lead to disorders in the synthesis and metabolism of intracellular nucleotides, which in turn affect key biological processes such as DNA synthesis and repair, and cellular signaling. A key driving factor for the onset and progression of breast cancer may be the aberrant activation of these pathways [32, 33].

Our future study on gene expression profiling analysis in relation to clinical efficacy and recurrence in Luminal A breast cancer allows us to make the following recommendations for guiding future therapy of this type of breast cancer. Greater survival and reduced recurrence rates were linked to increased expression of genes such GATA3, XBP1, FOXA1, TFF3, ESR1, and SCUBE2, according to our study. Patients with Luminal A breast cancer may benefit from improved efficacy and prognosis if more is learned about the functional mechanism of these genes and targeted therapeutic techniques are developed for them. Variations in gene expression characterize Luminal A breast cancer, which is characterized by its heterogeneity. Therefore, in the future, we can use Gene expression profiling analysis and other molecular markers to formulate individualized treatment plans for patients. By selecting the most appropriate therapeutic drug and dose according to the patient's Gene expression profiling, the therapeutic effect can be improved and unnecessary side effects can be reduced.

Considering the complexity and heterogeneity of Luminal A breast cancer, single drug treatment may not be able to completely control the growth and metastasis of the tumor. Therefore, in the future, a combination of multiple treatment strategies can be explored, such as combination chemotherapy, endocrine therapy, immunotherapy, etc., to enhance treatment effectiveness and reduce the risk of drug resistance and recurrence. Further preclinical validation and laboratory study are required to confirm the precise mechanism of these genes in Luminal A breast cancer, as our research results are based on the observation of gene expression profile analysis. Through animal models and cell experiments, it is possible to gain a deeper understanding of the functions of these genes and evaluate potential therapeutic targets and drug sensitivity.

In conclusion, by analyzing the Gene expression profiling of Luminal A breast cancer patients, we can identify genes related to clinical efficacy and recurrence, and provide a new direction for future treatment. The application of individualized treatment, targeting specific genes, combined treatment strategies and pre-clinical validation strategies is expected to improve the prognosis and survival rate of Luminal A breast cancer patients. Future research should continue to explore these directions in depth and strengthen cooperation to achieve more effective treatment strategies and personalized healthcare goals.

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***Ethical consideration*:** The research adhered strictly to ethical guidelines and principles. The [Name of Institutional Review Board or Ethics Committee] criteria were followed in all procedures involving human subjects. Every participant gave their informed consent, guaranteeing the privacy and confidentiality of their personal data.

***Author contribution*:** Each author's contribution to this study is acknowledged and recognized. Jiaxiang Ma was responsible for writing, Tieying Gan contributed to proofreading, and Ailing Song played a key role in review and ideation. The collaboration and combined efforts of all authors were essential for the successful completion of this research.

REFERENCES

1. Stashko C, Hayward MK, Northey JJ, *et al.* (2023) A convolutional neural network STIFMap reveals associations between stromal stiffness and EMT in breast cancer. *Nat Commun, **14**(1): 3561*.
2. Sanderson K (2023) Huge leap in breast cancer survival rate. Nature, 2023.
3. Yang Y, He Y, Fan Z, *et al.* (2023) Phase III study of HR-positive/HER2-negative/lymph node-positive breast cancer non-responsive to primary chemotherapy: a randomized trial. *NPJ Breast Cancer, **9**(1): 54*.
4. Zhang L, Mosquera I, Lucas E, *et al.* (2023) CanScreen5, a global repository for breast, cervical and colorectal cancer screening programs. *Nat Med, **29**(5): 1135-45*.
5. Sato G, Shirai Y, Namba S, *et al.* (2023) Pan-cancer and cross-population genome-wide association studies dissect shared genetic backgrounds underlying carcinogenesis. *Nat Commun, **14**(1): 3671*.

[DOI: 10.61186/ijrr.22.2.251]

6. Zhang J, Hu Z, Chung HH, et al. (2023) Dependency of NELF-E-SLUG -KAT2B epigenetic axis in breast cancer carcinogenesis. *Nat Commun,* ***14****(1): 2439*.
7. Sanchez-Vega F, Mina M, Armenia J, *et al.* (2018) Oncogenic signaling pathways in the cancer genome atlas. *Cell,* ***173****(2): 321-37.e10*.
8. Lee JJ, Jung YL, Cheong TC, *et al.* (2023) ERα-associated translocations underlie oncogene amplifications in breast cancer. *Nature,* ***618****(7967): 1024-32*.
9. Nolan E, Lindeman GJ, Visvader JE (2023) Deciphering breast cancer: from biology to the clinic. *Cell,* ***186****(8): 1708-28*.
10. Krug K, Jaehnig EJ, Satpathy S, *et al.* (2020) Proteogenomic landscape of breast cancer tumorigenesis and targeted therapy. *Cell,* ***183****(5):1436-56.e31*.
11. Abubakar M, Figueroa J, Ali HR, *et al.* (2019) Combined quantitative measures of ER, PR, HER2, and KI67 provide more prognostic information than categorical combinations in luminal breast cancer. *Mod Pathol, 32(9):1244-56*.
12. Kataoka M (2022) The Contribution of Imaging as a Prognostic Marker of Luminal Breast Cancer. *Radiology,* ***304****(2): 320-1*.
13. Wu Q, Tian P, He D, *et al.* (2023) SCUBE2 mediates bone metastasis of luminal breast cancer by modulating immune-suppressive osteoblastic niches. *Cell Res,* ***33****(6): 464-78*.
14. Kim I, Choi S, Kim S (2018) BRCA-Pathway: a structural integration and visualization system of TCGA breast cancer data on KEGG pathways. *BMC Bioinformatics,* ***19****(1): 42*.
15. Huang Y, Chen L, Tang Z, et al. (2021) A novel immune and stroma related prognostic marker for invasive breast cancer in tumor microenvironment: A TCGA based study. *Front Endocrinol (Lausanne),* ***12****: 774244*.
16. Gao C, Zhuang J, Zhou C, *et al.* (2019) SNP mutation-related genes in breast cancer for monitoring and prognosis of patients: A study based on the TCGA database. *Cancer Med,* ***8****(5):2 303-12*.
17. Serrano-López EM, Coronado-Parra T, Marín-Vicente C, *et al.* (2022) Deciphering the Role and signaling pathways of PKCα in luminalA breast cancer cells. *Int J Mol Sci,* ***23****(22)*.
18. Chen YH, Zhang TF, Liu YY, *et al.* (2022) Identification of a 5-gene-risk score model for predicting luminal A-invasive lobular breast cancer survival. *Genetica,* ***150****(5): 299-316*.
19. Guo Q, Qiu P, Yao Q, *et al.* (2022) Integrated bioinformatics analysis for the screening of hub genes and therapeutic drugs in androgen receptor-positive TNBC. *Dis Markers,* ***2022****: 4964793*.
20. Ahn S, Kwon A, Huh YH, et al. (2022) Tumor-derived miR-130b-3p induces cancer-associated fibroblast activation by targeting SPIN90 in luminal A breast cancer. *Oncogenesis,* ***11****(1): 47*.
21. Zhang Y, Wu H, Yu Z, *et al.* (2022) Germline variants profiling of BRCA1 and BRCA2 in Chinese Hakka breast and ovarian cancer patients. *BMC Cancer,* ***22****(1): 842*.
22. Hakkaart C, Pearson JF, Marquart L, *et al.* (2022) Copy number variants as modifiers of breast cancer risk for BRCA1/BRCA2 pathogenic variant carriers. *Commun Biol,* ***5****(1): 1061*.
23. Matta BP, Gomes R, Mattos D, *et al.* (2022) Familial history and prevalence of BRCA1, BRCA2 and TP53 pathogenic variants in HBOC Brazilian patients from a public healthcare service. *Sci Rep,* ***12****(1): 18629*.
24. Katheeja MN, Das SP, Das R, Laha S (2023) BRCA1 interactors, RAD50 and BRIP1, as prognostic markers for triple-negative breast cancer severity. *Front Genet,* ***14****: 1035052*.
25. Sanz-Moreno A, Palomeras S, Pedersen K, *et al.* (2021) RANK signaling increases after anti-HER2 therapy contributing to the emergence of resistance in HER2-positive breast cancer. *Breast Cancer Res,* ***23****(1): 42*.
26. Kast K, John EM, Hopper JL, *et al.* (2023) Associations of height, body mass index, and weight gain with breast cancer risk in carriers of a pathogenic variant in BRCA1 or BRCA2: the BRCA1 and BRCA2 Cohort Consortium. *Breast Cancer Res,* ***25****(1): 72*.
27. Ashekyan O, Abdallah S, Shoukari AA, *et al.* (2022) Spotlight on Exosomal Non-Coding RNAs in Breast Cancer: An In Silico Analysis to Identify Potential lncRNA/circRNA-miRNA-Target Axis. *Int J Mol Sci,* ***23****(15)*.
28. Subramanian A, Tamayo P, Mootha VK, *et al.* (2005) Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc Natl Acad Sci USA,* ***102*** *(43):15545-50*.
29. Dennis G, Jr., Sherman BT, Hosack DA, *et al.* (2003) DAVID: Database for annotation, visualization, and integrated discovery. *Genome Biol,* ***4****(5): P3*.
30. Rey-Vargas L, Bejarano-Rivera LM, Mejia-Henao JC, *et al.* (2022) Association of genetic ancestry with HER2, GRB7 AND estrogen receptor expression among Colombian women with breast cancer. *Front Oncol,* ***12****: 989761*.
31. Asif K, Memeo L, Palazzolo S, Frión-Herrera Y, *et al.* (2021)STARD3: A prospective target for cancer therapy. *Cancers (Basel),* ***2021****: 13 (18)*.
32. Wang B, Wu L, Chen J, *et al.* (2021) Metabolism pathways of arachidonic acids: mechanisms and potential therapeutic targets. *Signal Transduct Target Ther,* ***6****(1): 94*.
33. Yao X, Li W, Fang D, *et al.* (2021) Emerging roles of energy metabolism in ferroptosis regulation of tumor cells. *Adv Sci (Weinh),* ***8****(22): e2100997*.

[DOI: 10.61186/ijrr.22.2.251]