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Identification and strategies for triple-negative breast cancer subtypes

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ABSTRACT

Triple-Negative Breast Cancer (TNBC) is a subtype of Breast Cancer (BC) with high mortality, early recurrence, more frequent, poor prognosis, and comparative data have shown that women with the TNBC phenotype have a 5-year overall 19 % survival lower and 18% lower disease-free survival than non-TNBC counterparts. The purpose of this study is to find out some of the identification and strategic management of Triple Negative Breast Cancer (TNBC). This research method used descriptive qualitative through the Systematic Literature Review (SLR) approach. The identifications obtained seven TNBC subtypes categorized and labeled differently such as Basal-Like 1 (BL1), Basal-Like 2 (BL2), Immunomodulatory (IM), Mesenchymal (M), Mesenchymal Stem–Like (MSL), Luminal Androgen Receptor (LAR), and Unstable (UNS). The strategy used the Development of a Breast Cancer Prediction Model with PPI Data and Support Vector Machines, Robust Identification of Target Genes and Outliers in TNBC data, and Sensitivity of Cell Lines to Heat Shock Protein 90 Inhibitor (Hsp90i). Based on the several strategies that have been described, there are various kinds of tests to determine TNBC according to the needs of each test. However, there is still no optimal solution that is suitable for all conditions.

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INTRODUCTION

As of the end of 2020, there were 7.8 million living women diagnosed with breast cancer in the last 5 years, and it makes the most common cancer in the world. Triple-Negative Breast Cancer (TNBC) is a subtype of Breast Cancer (BC) with high mortality, early recurrence, more frequent, and poor prognosis. Comparative data have shown that women with the TNBC phenotype have a 5-year overall survival 19% lower and 18% lower disease-free survival than non-TNBC counterparts (Nwagu *et al.*, 2022).

TNBC is caused by the absence of detectable Estrogen Receptor (ER) and Progesterone Receptor (PR) expressions and lack of amplification of the Human Epidermal Growth Factor 2 (HER-2) receptor gene (Brian D Lehmann, 2014). The potential risk factors for TNBC can be divided into non-modifiable and modifiable risk factors. A non-modifiable risk factor is age, about

80% of breast cancer (including TNBC) are >50 years old. The risk of cancer will increase with age, with the risk of 1.5% at the age of 40 years, 3% at the age of 50 years, and more than 4% at the age of 70 years old (Mallika Siva Donepudi & Kondapalli, Seelam Jeevan Amos, 2014). Sex, women have breast cells that are very susceptible to the hormones estrogen and progesterone, as well as an imbalance in circulating estrogens and androgens which is associated with an increased risk of breast cancer (Hormones *et al.*, n.d.); genetic mutations in genes, such as BRCA1 and BRCA2 were found to be highly associated with TNBC (Shiovitz & Korde, 2015); race, the incidence of TNBC remains high among non-Hispanic white women (Id *et al.,* 2019), and breast tissue density, postmenopausal and premenopausal women breast density affect the cancer risk, i.e. the higher the density, the higher the probability this disease occurs (Checka, Cristina M, Jennifer E. Chun, Freya R. Schnabel, Jiyon Lee, n.d.).

One of the potentially modifiable risk factors for TNBC is Diethylstilbestrol medicine, which is the main cause of breast cancer during pregnancy. The risk of breast cancer increases with increasing doses of diethylstilbestrol. This correlation was observed with diethylstilbestrol uptake even without estrogen and progesterone receptor expression (Adam *et al.*, 2011). Physical activity reduces exposure to endogenous sex hormones and can also alter insulin-like growth factor-1 levels and immune response (Hormones *et al.*, n.d.). Alcohol is considered to increase the risk of developing cancer (Shield *et al.*, 2016). Not enough for vitamin supplements. Research is being conducted to evaluate the risk of cancer by taking vitamins, particularly the B, C, and E folic acid vitamins, and multivitamins. Vitamin D supplementation, namely high serum 25-hydroxyvitamin D, is considered a potential cancer control agent in postmenopausal women and the premenopausal period (Almansour, 2022). Exposure of the mammary glands to the chemicals Polychlorinated Biphenyl (PCB) and Dichlorodiphenyltrichloroethane (DDT) increases the risk of breast cancer. Women who have been exposed to carcinogenic chemicals are at increased risk of developing breast cancer and epigenetic changes and mutations. Besides, exposure and duration contribute to an increased risk of breast cancer mutagenesis (Veruscka Leso *, Maria Luigia Ercolano, 2019).

This study aims to determine the identification and the latest diagnostic or treatment strategies related to triple-negative breast cancer through a literature review journal.

RESEARCH METHOD

This research method used descriptive qualitative using the Systematic Literature Review (SLR) approach. This is a type of review article whose aim is to find evidence of clinical efficacy (evidence-based) of a problem to get suggestions for problem-solving. The data sources involved secondary sources from journals and books (Ramdhani *et al.*, 2014). The data collection method is through the documentation by searching and digging data from journals/books that are relevant to documents related to TNBC identification and strategy. Data analysis used annotated bibliographic analysis (Mudavanhu, 2017).

RESULTS AND DISCUSSIONS

Seven TNBC subtypes are categorized and labeled differently, Basal-Like 1 (BL1); Basal-Like 2 (BL2); Immunomodulatory (IM); Mesenchymal (M); Mesenchymal Stem–Like (MSL); Luminal Androgen Receptor (LAR); and Unstable (UNS) (Lehmann *et al.*, n.d.). These types are categorized based on their gene expression portfolio, for example, the similarity between BL-1 and BL-2 is substantial gene expression during cell division as well as cell cycle advancement. Nevertheless, BL-1 retains high gene expression related to DNA response pathways, including DNA repair and DNA replication activity. Whereas, BL-2 displays high expression in growth factor signaling, alternatively, Immunomodulatory (IM) has high gene expression that is related to immune cell processes, specifically natural killer cell pathways, TH1/TH2 pathways, cytokine signaling, B cell

receptors (BCR), and antigen processing. In addition, the Mesenchymal Stem-Like and Mesenchymal subtypes are unquestionably understood to have high expression of genes related to extracellular receptor interactions, cell motility, and cell differentiation pathways. Apart from that, MSL shows significant differences from the mesenchymal subtype, in which MSL has low expression of claudin (3, 4, 7) genes (Lehmann *et al.*, n.d.). Consequently, the MSL subtype categorized as a claudin-low tumor was found by Herschkowitz *et al*. Lastly, the LAR subtype shows high expression of genes related to hormonally regulated pathways and genes regarding the androgen receptor and its co-activators (Lehmann *et al.*, n.d.).

Most TNBCs are basal-like subtypes and many basal-like breast cancers are triple negative. They are not equivalent in terms of gene expression tagging and IHC (Immunohistochemistry) analysis. Breast cancers, such as basal, are a classification based on gene expression profiles. Although they appear identical, there is a discrepancy of up to 30% between both groups. Besides low expression of ER, PR, and HER2, basal-like breast cancers are characterized by expression of CK5, CK14, caveolin-1, caix, p63, EGFR (Epidermal Growth Factor Receptor) High /HER1, which is reflected in the basal cell/myoepithelial component of the mammary gland (Finetti *et al*., 2009).

TNBC is notorious for its aggressive behavior and is characterized by a younger age of onset, a high average tumor size, higher grade tumors, and sometimes, higher nodal positivity rates (Dent *et al*., 2007). In addition, this group is also known for its peak of early recurrence between the first and third year after diagnosis and more aggressive metastases which are more likely to occur in the liver, especially in the lungs and brain, which are less likely to spread to the bone (Criscitiello *et al*., 2012). Based on histological findings, the majority of triple-negative breast cancers are of ductal origin. However, several other aggressive phenotypes are also seen in excess, including metaplastic, apocrine, and adenoid cystic (Milanezi *et al*., 2006). A histological study of basal-like tumors, all ER/HER2 negative, yielded increased mitotic count, and geographic necrosis, pushed to the limit of invasion and stromal lymphocytic response (Livasy *et al*., 2006).

Triple-negative breast cancer (TNBC) is a special subtype of breast cancer that is difficult to treat. It is very important to identify breast cancer-associated genes that can provide new biomarkers for breast cancer diagnosis and potential treatment goals. Identification of disease-associated genes and prediction of high-risk breast cancer patients has become an important issue. Genes highly related to TNBC can be found using gene expression profiling. However, there are still some problems in the current protein function prediction methods using high protein interaction data. Usually, it has a high rate of false positives and reduced reliability of functional predictive results (Oliver *et al.*, 2015).

In recent years, the continuous accumulation of protein interaction data has made it possible to analyze and predict protein function at the system level via protein-protein interaction (PPI) networks. Proposing the "guilt by association rule" (GBA) which states that interacting proteins have the same or similar functions, indicating that protein function can be predicted by protein interactions (Nabieva *et al.*, 2005)

Identification of the TNBC Gene and Development of a New High-Risk Breast Cancer Prediction Model based on PPI Data and Support Vector Machines aims to develop a new high-risk breast cancer prediction model, seven raw gene expression data sets from the NCBI Gene Expression Omnibus (GEO) database (GSE31519, GSE9574, GSE20194, GSE20271, GSE32646, GSE45255, and GSE15852). This study used the Maximum Relevance Minimum Redundancy (mRMR) method and selected significant genes. Then, mapping gene transcripts on the Protein-Protein Interaction (PPI) network from the Search Tool for the Retrieval of Interacting Genes (STRING) was conducted, as well as tracing the shortest path between each protein pair. Genes with higher intermediate values were selected from the shortest protein pathways and permutation tests were performed to determine validity and precision. The potential genes related to TNBC used in the study were 14 out of 54 genes. The results obtained by the new SVM (Support Vector Machine) method based on C-SVC (Cost Support Vector Classification) are the prediction accuracy of normal tissue and TNBC network

reached 95.394%, and prediction of TNBC Stage II and Stage III reached 86.598%, indicating that the gene plays an important role in differentiating breast cancer and that the method can hold promise in practical use (Li *et al.*, 2019).

CONCLUSION

Based on the several strategies that have been described above, there are various kinds of tests to determine TNBC according to the needs of each test. However, there is still no one-size-fits-all optimal solution, such as the case of the Hsp90i trial, for initial results requiring additional post hoc analysis of human tumours from completed Hsp90i clinical trials, which may provide further insight into the clinical utility of transcription/protein classifiers to predict drug sensitivity. The success of future clinical trials depends on investigators disentangling the heterogeneity of TNBC and will proceed with multi-institutional stratification of patients with subtype/pathway-specific genomic alterations to align molecular states with appropriate therapy.

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