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Integrative Bioinformatics and Statistical Approaches for Identifying Prognostic Biomarkers and Therapeutic Targets in Breast Cancer

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A B S T R A C T

Breast cancer is a leading cause of cancer-related mortality worldwide, necessitating the identification of reliable biomarkers for prognosis and targeted therapy. This study employed an integrative bioinformatics and statistical approach to analyze differentially expressed genes (DEGs) in breast cancer using datasets GSE70947 and GSE22820 from the gene expression omnibus (GEO). A protein-protein interaction (PPI) network was constructed to identify hub genes, followed by functional enrichment analysis to determine their biological significance. Survival analysis using the KMplot database revealed that CDC45, KIF2C, CCNB1, KIF4A, CENPE, CHEK1, KIF15, AURKB, NCAPG, and HJURP were significantly associated with poor prognosis. These genes were primarily enriched in cell cycle regulation, mitotic spindle organization, and DNA damage response, highlighting their role in tumor progression. Among them, CCNB1, CHEK1, and AURKB were strongly linked to cell cycle progression and checkpoint regulation, while KIF2C and CENPE played essential roles in mitotic division. High expression levels of these genes correlated with reduced overall survival, suggesting their potential as prognostic biomarkers and therapeutic targets in breast cancer.These discoveries help us better understand how breast cancer develops and point to potential targets for tailored treatments.

Keywords: Breast cancer, Prognostic biomarkers, Protein-protein interaction, Survival analysis, Cell cycle regulation.

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1. Introduction

Globally, multiple cancerous diseases remain the primary source of cancer cases and deaths with extraordinary incidences and deaths owing to considerable molecular diversity [1][2][3]. While strides in early diagnosis and targeted therapies have improved outcomes, the clinical variability of the disease arising from differing genomic profiles, therapeutic resistance, and aggressive behavior in metastasis

urges us into an in-depth journey into genomics. Radiomic/transcriptomic characterization of late-stage cancers allows one to map an entire set of differentially expressed genes associated with their pathogenesis [4][5][6]. Teaming these technologies with systems biology tools opens doorways to discover new biomarkers and mechanistic drivers that could represent rational paths for precision oncology [7][8][9].

Differentially gene expression analysis focuses on those genes aberrantly expressed in tumor versus normal tissues [10]. Such actors as the limma algorithm allow one to magnify this particular process, whereas the main goal of the analysis is to extract from noise those interesting candidates [11]. Gene lists only link up through intricate molecular crosstalk, fueling tumor evolution. This is when protein-protein interaction (PPI) networks come into the equation, providing important insight into functional hubs in cancer pathways. The highly connected nodes of such networks serve as central regulators of processes extending from growth to metastasis [12].

To identify the biological process these hubs, functional enrichment analyses-a generous inclusion spanning Gene Ontology and KEGG pathways-can uncover their functional roles in defining processes such as cell cycle control, DNA repair, and immunoediting. Such pathways, repeatedly usurped in breast cancer, support traits such as uncontrolled proliferation and genomic chaos [13][14]. These modules highlight mechanisms dictating the disease and illustrate pathways of vulnerability that could be targetable with therapeutics.

The prognostic validation is important in prediction of biomarker, it is can help to incorporate gene expression into clinical outcomes and provide survival analyses to isolate potential true multipliers or biomarkers [15][16][17]. For instance, target genes whose overexpression may correlate with poor survival could serve as dual prognostic indicators and therapeutic targets for bridging the insights from laboratory. This study uses well-documented techniques such as Gene Ontology (GO) analysis, protein-protein interaction (PPI) networks, and Kaplan-Meier (KM) plot analysis to investigate mechanisms of breast cancer. In contrast to the majority of sophisticated methods that are devoid of cross-validation and translational, this study fills such gaps by employing robust bioinformatics tools. Its major contribution lies in the discovery of the genomic origin of breast cancer and the conversion of omics data into solutions with an emphasis on patient care, thus enhancing both basic knowledge and clinical utility for better diagnostics and therapies.

2. Research Methods

This study employs a structured workflow integrating bioinformatics and statistical methods to analyze breast cancer gene expression data, from DEG identification to functional and clinical validation. A summary of our methodological steps can be found on Figure 1.

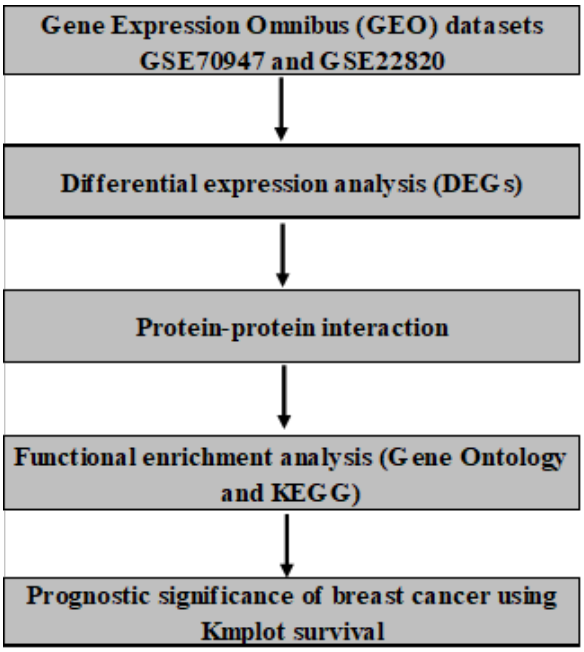

Figure 1. Study flowchart. Gene Expression Data Acquisition and Preprocessing, DEGs analysis, PPIs, gene ontology, KEGG and kmplot survival.

2.1. Differentially Expressed Genes (DEGs)

We analyzed DEGs regarding breast cancer through the application of transcriptomic datasets GSE70947 and GSE22820 using the limma package [18]. These analyses were conducted within a formal statistical framework. Raw microarray data underwent methodical preprocessing, which involved adjusting for background noise, applying quantile normalization to eliminate technical variation, and logarithmic transformation base 2 to stabilize variance. A gene-wise linear modeling approach was implemented to assess expression variation, with empirical Bayes moderation applied for the refinement of variance estimates and thus gave the expected boost in detection power to catch subtle transcriptional changes. To ensure factual occupancy representation of the results, significance threshold was stringently adhered, where DEGs were determined from the P-value of FDR < 0.05 (Benjamini-Hochberg) using the log fold change cut-off of $|\log(\text{FoldChange})| > 1$; thus, a balance of biological relevance and statistical plausibility was offered. This framework of cut-off helped to minimize type I errors and put genes showing notable expression changes in the forefront [18]. The analysis pipeline effused detection sensitivity for modest expression changes on the one hand and specificity against nonspecific claims founded on chance alone with a DEG listing of high confidence for follow-ups with functional validation.

$$Y = X\beta + \varepsilon$$

where:
Y represents the gene expression matrix,
X is the design matrix describing experimental conditions,
β denotes the coefficients corresponding to different conditions, and
ε is the random error term following a normal distribution.

2.2. Identification of Hub Genes through Protein-Protein Interaction Network Analysis

A protein-protein interaction network pool of the DEGs was established through STRING [19], with improvement on data visualization using Cytoscape [20]. The most significant most hub-important networks, which included all the nodes interacting with the highest number of nodes, were characterized by degree centrality analysis [21]. Such analysis allowed for the precise quantification of a gene's influence among members of its interacting neighbors through the number of direct contacts (v), with particular stress placed upon those plasma membrane genes central to the molecular signaling cascades.

$$D(v) = \sum_{i=0}^{n} A(v,i)$$

where:
$D(v)$ represents the degree centrality of node v,
$A(v,i)$ is the adjacency matrix, where 1 denotes a connection and 0 indicates no connection,
$D(v)$ is the total number of genes in the network.

2.3. Functional Annotation of Hub Genes via Gene Ontology Enrichment

Biological functions of hub genes were discerned using Gene Ontology enrichment analysis using the ClusterProfiler toolkit [22]. Genes were systematically classified into Biological Processes, Cellular Components, and Molecular Functions. Statistical significance of enriched terms was evaluated employing the hypergeometric distribution [23], highlighting pathways and mechanisms pivotal to disease pathogenesis.

$$P = 1 - \sum_{i=1}^{k-1} \frac{\binom{M}{i}\binom{N-M}{n-i}}{\binom{N}{n}}$$

where:
N is the total number of genes in the genome,
M represents the total number of genes associated with a specific GO term,
n is the number of DEGs in the study, and
k is the number of DEGs annotated to the specific GO term.

2.4. Prognostic Evaluation of DEGs via Kaplan-Meier Survival Analysis

The clinical relevance of key DEGs in breast cancer prognosis was assessed using the KMplot platform [24], which aggregates transcriptomic and clinical data from TCGA, GEO, and EGA repositories. Survival curves stratified by gene expression levels revealed associations between DEGs and patient outcomes, identifying potential biomarkers predictive of survival.

3. Result and Discussion

3.1. Identification of Differentially Expressed Genes (DEGs)

Analysis of transcriptomic profiles from the GSE70947 and GSE22820 datasets uncovered markedly distinct expression dynamics, visualized through volcano plots **(Figure 2A-B)**. These plots delineated upregulated transcripts (red), downregulated candidates (blue), and non-significant features (gray), with GSE70947 encompassing 9,356 analytes and GSE22820 comprising 19,537 variables. Both datasets exhibited robust differentially expression signals, with numerous genes surpassing significance thresholds, including pivotal regulators implicated in disease pathways.

Cross-dataset comparative interrogation via Venn diagrams **(Figure 2C-D)** further revealed a conserved core of dysregulated genes. Strikingly, 59 upregulated ($\log2FC > 1$) and 79 downregulated

(log2FC < -1) genes overlapped between the two cohorts, suggesting their potential role as master regulators. This convergence of DEGs across independent datasets underscores their biological plausibility, positioning them as high-priority targets for functional validation in subsequent mechanistic studies.

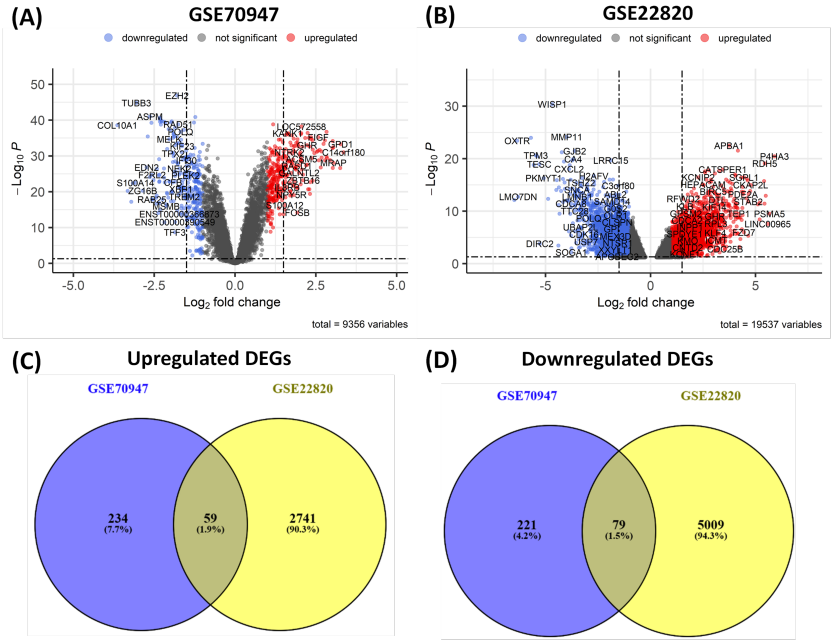

Figure 2. Identification of differentially expressed genes (DEGs) across GSE70947 and GSE22820 datasets. **(A-B)** Volcano plots display transcriptomic profiles, with red and blue markers denoting upregulated (log2FC >1) and downregulated (log2FC <-1) genes, respectively, against a backdrop of non-significant hits (gray). GSE70947 and GSE22820 contained 9,356 and 19,534 transcripts, respectively. **(C-D)** Comparative Venn analysis revealed 138 overlapping DEGs, comprising **(C)** 59 genes showing conserved upregulation and **(D)** 79 with persistent downregulation across both cohorts. These shared signatures, resilient to dataset-specific noise, underscore their potential as key biological mediators in disease pathogenesis.

3.2. Identification of Key Hub Genes in the PPI Network

Protein-protein interaction (PPI) network analysis of breast cancer-associated differentially expressed genes (DEGs) revealed critical regulatory hubs through connectivity-based ranking using the degree method **(Figure 3)**. Ten genes—CDC45, KIF2C, CCNB1, KIF4A, CENPE, CHEK1, KIF15, AURKB, NCAPG, and HJURP—emerged as top network hubs **(Table 1)**, demonstrating central roles in tumorigenic signaling cascades.

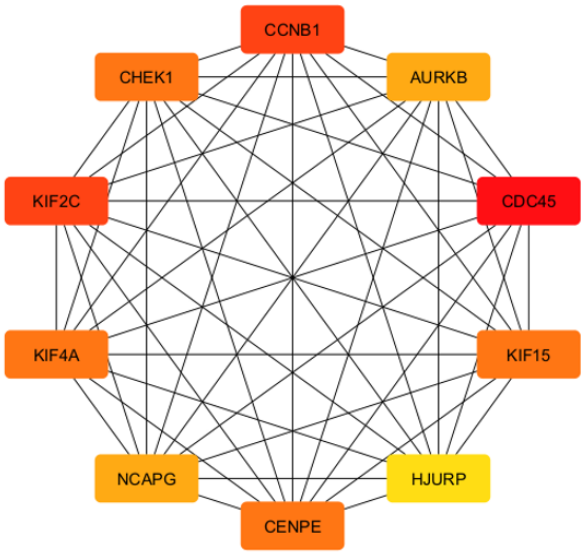

Figure 3. PPI network analysis of DEGs for key gene selection. The top ten most significant upregulated and downregulated gene clusters were identified from the PPI network using the degree method.

CDC45, a DNA replication initiator, drives tumor proliferation and invasiveness when overexpressed [25][26]. KIF2C, a mitotic spindle regulator, induces chromosomal instability through microtubule dynamics disruption [27][28]. CCNB1 governs G2/M transition, with elevated expression correlating to unchecked cell cycle progression and adverse clinical outcomes [29]. KIF4A, critical for chromosomal segregation, accelerates metastasis and therapy resistance [30], while CENPE ensures kinetochore-microtubule fidelity, with dysregulation promoting aneuploidy [31]. CHEK1, a DNA damage checkpoint kinase, mediates therapy resistance by preserving genomic integrity under stress [32].

Table 1. Ranking of the Top Ten Key Genes Identified from the PPI Network

Rank	Name	Score
1	CDC45	31
2	KIF2C	30
3	CCNB1	30
4	KIF4A	29
5	CENPE	29
6	CHEK1	29
7	KIF15	29
8	AURKB	28
9	NCAPG	28
10	HJURP	27

KIF15 stabilizes mitotic spindles, conferring paclitaxel resistance [33], whereas AURKB overexpression disrupts chromosomal condensation, fueling genomic instability in aggressive subtypes [34]. NCAPG, a condensin complex component, enhances chromatin compaction to drive proliferation [35], and HJURP maintains centromere integrity, with aberrant expression linked to poor prognosis [36]. Collectively, these hubs orchestrate tumor growth, metastatic dissemination, and therapeutic evasion, positioning them as promising diagnostic biomarkers and intervention targets.

3.3. Functional Enrichment Analysis of Key Genes

Functional enrichment analysis highlighted the predominant involvement of these DEGs in cell cycle control, mitotic spindle dynamics, and DNA repair mechanisms **(Table 2)**. CCNB1, CDC45, and CHEK1 were tightly linked to checkpoint regulation and cell cycle progression [37][38][39][40], while AURKB, KIF4A, and CENPE modulated chromosomal stability through microtubule-kinetochore interactions [41][42]. These pathways underpin tumorigenesis by sustaining proliferative signaling, evading growth suppression, and enabling metastatic spread—findings consistent with prior mechanistic studies.

Table 2. Significantly Enriched GO Functions and KEGG Pathways of Key Genes

GO Terms/Function	P-value	Associated Key Genes
GO Terms of Biological Process (BPs)		
Mitotic Spindle Organization (GO:0007052)	6.26E-08	CENPE;CCNB1;KIF4A;AURKB
Regulation Of Mitotic Cell Cycle Spindle Assembly Checkpoint (GO:0090266)	3.05E-05	CCNB1;AURKB
Regulation Of Cell Cycle Process (GO:0010564)	3.11E-05	CHEK1;KIF2C;AURKB
Cell Cycle G2/M Phase Transition (GO:0044839)	1.74E-04	CCNB1;AURKB
DNA Integrity Checkpoint Signaling (GO:0031570)	1.92E-04	CDC45;CHEK1
GO Terms of Cellular Components (CCs)		
Microtubule (GO:0005874)	1.56E-08	CENPE;KIF4A;KIF2C;AURKB;KIF15
Spindle (GO:0005819)	2.36E-06	CENPE;KIF4A;KIF2C;AURKB
Condensed Chromosome (GO:0000793)	3.03E-06	CENPE;CHEK1;NCAPG
Spindle Microtubule (GO:0005876)	4.43E-06	CENPE;KIF4A;AURKB
Nuclear Chromosome (GO:0000228)	1.22E-05	CDC45;CHEK1;NCAPG
GO Terms of Molecular Function (MFs)		
Microtubule Binding (GO:0008017)	1.90E-04	CENPE;KIF2C;KIF15
Tubulin Binding (GO:0015631)	4.56E-04	CENPE;KIF2C;KIF15
Patched Binding (GO:0005113)	0.0030	CCNB1
Microtubule Plus-End Binding (GO:0051010)	0.0095	KIF2C
Protein Serine/Threonine Kinase Activity (GO:0004674)	0.0120	CHEK1;AURKB
Kyoto Encyclopedia of Genes and Genomes (KEGGs)		
Cell cycle	2.70E-05	CCNB1;CDC45;CHEK1
p53 signaling pathway	5.80E-04	CCNB1;CHEK1
Cellular senescence	0.0026	CCNB1;CHEK1

Clinically, these genes hold dual significance as prognostic indicators and therapeutic vulnerabilities. Overexpression of CCNB1, AURKB, and CHEK1 may stratify high-risk patients, while targeting KIF2C or KIF4A could synergize with microtubule-targeting agents like paclitaxel. CHEK1's role in p53-mediated DNA repair further suggests its inhibition could counteract therapy resistance. This functional convergence underscores their utility in precision oncology, offering avenues for biomarker-driven diagnostics and combinatorial treatment strategies tailored to disrupt core oncogenic networks.

3.4. Survival Analysis of Key Hub Genes in Breast Cancer

Kaplan-Meier survival analysis was performed to evaluate the prognostic significance of key hub genes in breast cancer. The survival curves demonstrate that patients with high expression levels of CDC45, KIF2C, CCNB1, KIF4A, CENPE, CHEK1, KIF15, AURKB, NCAPG, and HJURP have significantly worse overall survival compared to those with low expression levels **(Figure 4)**. The hazard ratio (HR) values range from 1.24 to 1.83, with log-rank p-values < 0.05, indicating a strong association between elevated gene expression and poor prognosis. The shorter survival times observed in patients with overexpression of these genes suggest their involvement in promoting tumor aggressiveness, increased proliferation, and resistance to apoptosis. These findings highlight their potential

role as indicators of poor clinical outcomes in breast cancer patients. This suggests that overexpression of these genes is strongly associated with adverse clinical outcomes, such as an increased risk of recurrence and metastasis.

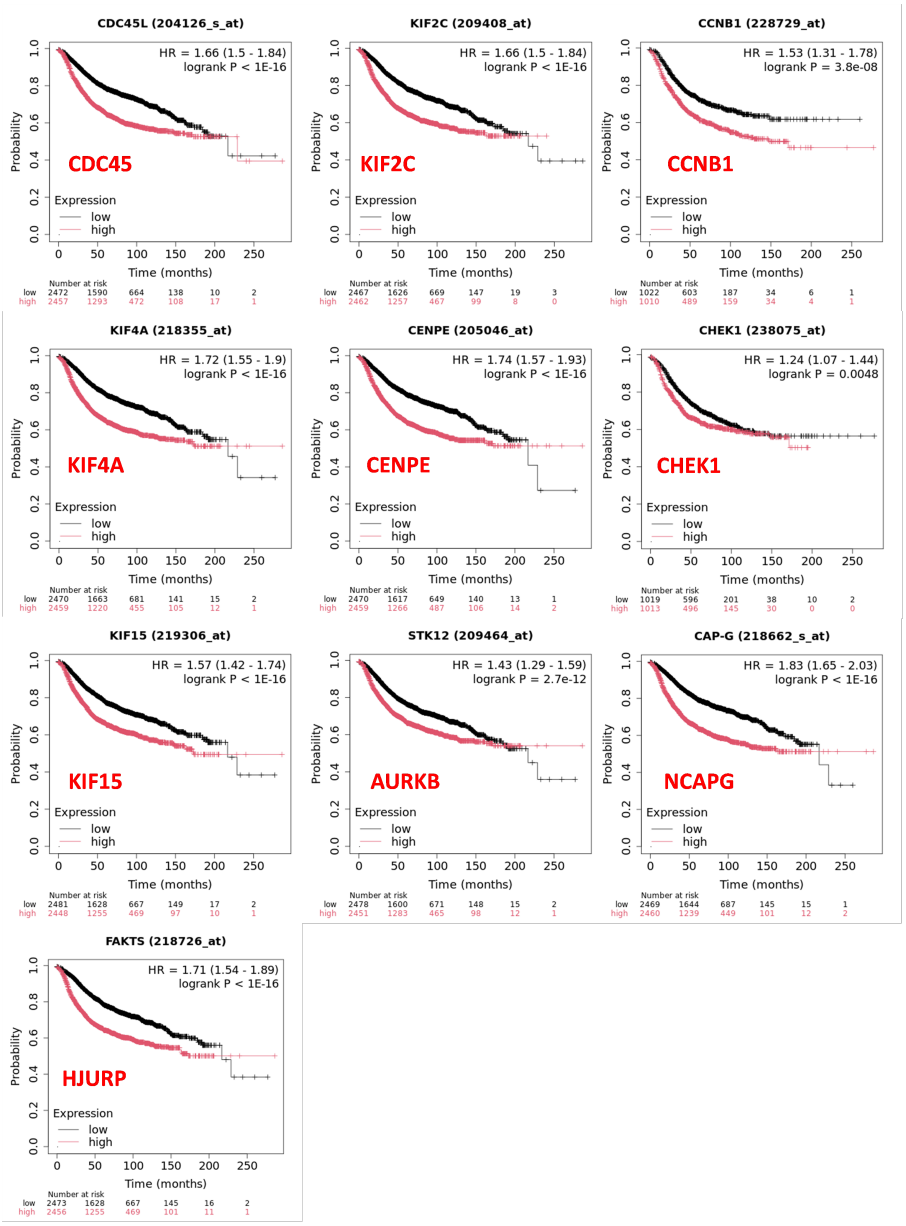

Figure 4. Prognostic Significance of Key Hub Genes in Breast Cancer. The hazard ratio (HR) is a relative measure to prognose the outcome of breast cancer patients. The logrank p-value was used to assess the prognostic significance and the cut off was set at < 0.05 for statistical significance to determine whether there was a significant difference in the prognostic outcomes of breast cancer patients.

4. Conclusion

Our study identified CDC45, KIF2C, CCNB1, KIF4A, CENPE, CHEK1, KIF15, AURKB, NCAPG, and HJURP as key genes overexpressed in breast cancer and significantly associated with poor prognosis. Functional enrichment analysis revealed their crucial roles in cell cycle regulation,

mitotic spindle organization, and DNA damage repair, highlighting their involvement in uncontrolled proliferation and genomic instability. Among them, CCNB1, CHEK1, and AURKB were strongly linked to cell cycle progression and checkpoint regulation, while KIF2C and CENPE played vital roles in mitotic division. Survival analysis further confirmed that high expression of these genes correlates with reduced overall survival, suggesting their potential as prognostic biomarkers and therapeutic targets for breast cancer.

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