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RESEARCH ARTICLE

Role of Fibroblast Growth Factor Pathway Receptor Genes in Breast Cancer

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Abstract This study investigates the role of the Fibroblast Growth Factor (FGF) Pathway in breast cancers at the RNA expression level. Key cancer-related genes within the FGF pathway were analysed using datasets containing RNA and clinical information for breast cancer patients. The study involved 266, 289, and 2089 patient samples across different datasets. Various statistical tests, including Kaplan-Meier Test, Chi-Square Test, overall survival, and disease-free survival analysis, were conducted using tools such as BRB array and IBM SPSS Statistics. Associations between RNA expression and clinicopathological features were identified, such as FGFR1 being linked to early-stage grades and FGFR1OP associated with late-stage grades. Expression patterns of specific genes were also correlated with different cancer statuses. Surprisingly, survival analysis revealed contradictory findings, with FGFR1OP2 and FGF2 associated with poor overall survival, FGFR2 with good survival, and FGFR1OP2 linked to poor disease-free survival in breast cancer. These inconsistencies emphasize the necessity of additional study to better understand the dual roles of FGF pathway genes in cancer progression.

Keywords: FGF pathways, breast cancer, clinical information, Kaplan-Meier test, Chi-Square test, BRB array, IBM SPSS, FGFR1, FGFR1OP2, FGF2, FGFR2, cancer progression.

Introduction

Cancer initiation in the breast results from the uncontrolled growth of normal cells, leading to the formation of tumors [1]. Metastasis, the spread of cancer to additional body parts, is a characteristic feature of breast cancer [2]. Tumors can be classified as malignant, with the potential to be harmful, or benign, posing no threat to health [3]. Malignant tumors can spread through blood vessels, a process known as metastasis, while benign tumors do not exhibit this capability [4]. The advanced stage, where breast cancer has spread to other parts of the body, is termed stage four [5].

Globally, breast cancer in female has become more commonly diagnosed than other cancer such as Lung cancer [6]. In 2020, about 2,261,419 new case of breast cancer were identified worldwide [7]. The most common cancer in women to receive a diagnosis in the US is breast cancer [8]. In 2023, it is estimated that 297,790 women in the United States had been identified with invasive breast cancer, whereas 55,720 had received a diagnosis of non-invasive breast cancer [9]. Since the mid-2000s, the incidence of invasive breast cancer in female has elevated by about 0.5% annually, as well as due to higher overall body weight, reduced fertility rates and a rise in the average age of new mothers [10]. Furthermore, It is estimated that 2,800 men in the US would receive an invasive breast cancer diagnosis in 2023 [11]. It is evaluated that 43,700 cause to death in the United States including 43,170 women and 530 men [12]. Globally, women breast cancer is the 5th leading cause of death, with an approximately 684,996 women succumbing to the disease in 2020 [13]. In the US, more than 3.8 million women either have breast cancer or are suffering with it [8]. However, it is most commonly diagnosed in middle-aged and older women. Approximately 6.6% of breast cancer cases are identified in women under 40 years old, with 2.4% in those under 35 and 0.65% in women under 30. Whereas, in the Middle East, breast cancer stands out as a common malignancy among women [14]. Frequency rates vary, with higher incidence in North American and Northern European nations, intermediate rates in Southern and Eastern European and South American countries, and lower rates in Asia and Africa. Notably, there has been a rapid increase in breast cancer incidence rates in developing nations [15]. In the United Kingdom, it holds

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the highest age-standardized incidence and mortality rates globally [16]. The disease is the leading cause of death among females aged 40-50, with an increasing incidence observed among women aged 50-65 due to breast screening in this age group [17]. The statistical analyses indicate a decline in breast cancer mortality rates during the 1990s in developed countries, attributed to mammography screening [18]. However, by 2000, there was insufficient evidence supporting the mortality-reducing impact of screening [19]. Some reviews suggest that breast cancer mortality may be a misleading outcome measure, and supplemental Cochrane reviews emphasize the potential for screening to lead to more aggressive treatment [20].

Breast cancer risk factors worldwide include hormonal changes, supplementary hormone use, and the timing and number of pregnancies [21]. Women who have their first full-term pregnancy after 30 or who never experience full-term pregnancy face a higher risk due to increased exposure to progesterone and estrogen during the menstrual cycle. Pregnancy reduces the number of menstrual cycles and lifetime hormonal exposure [22].

While cancer is predominantly a genetic disease, various genetic mechanisms contribute to its initiation and progression. These mechanisms include small-scale sequence variations (e.g., SNPs), insertions and deletions (Indels), large-scale structural mutations (e.g., copy number variations, chromosomal rearrangements), and RNA dysregulation [23]. Genomic variants may act in cis, affecting their own expression, or in trans, influencing genes at other genomic sites [24]. Mapping copy number variation, copy number aberrations, and single nucleotide polymorphisms in the breast cancer genome helps distinguish germ-line from somatic variants and analyse their impact on expression shown in figure 1 [25].

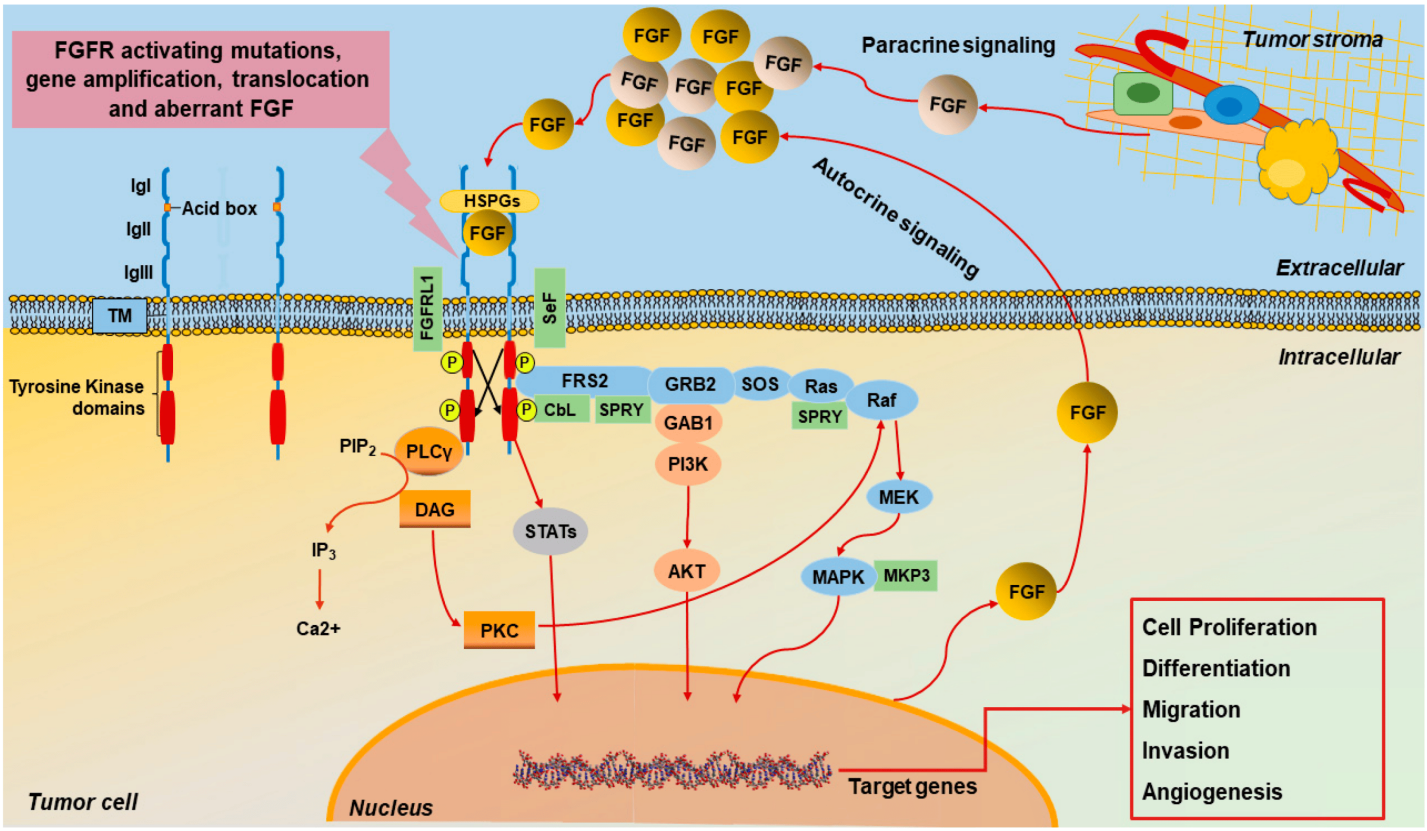


Figure 1. Fibroblast growth factor receptor (FGFR) signaling pathway, spotlight its role in cancer pathogenesis

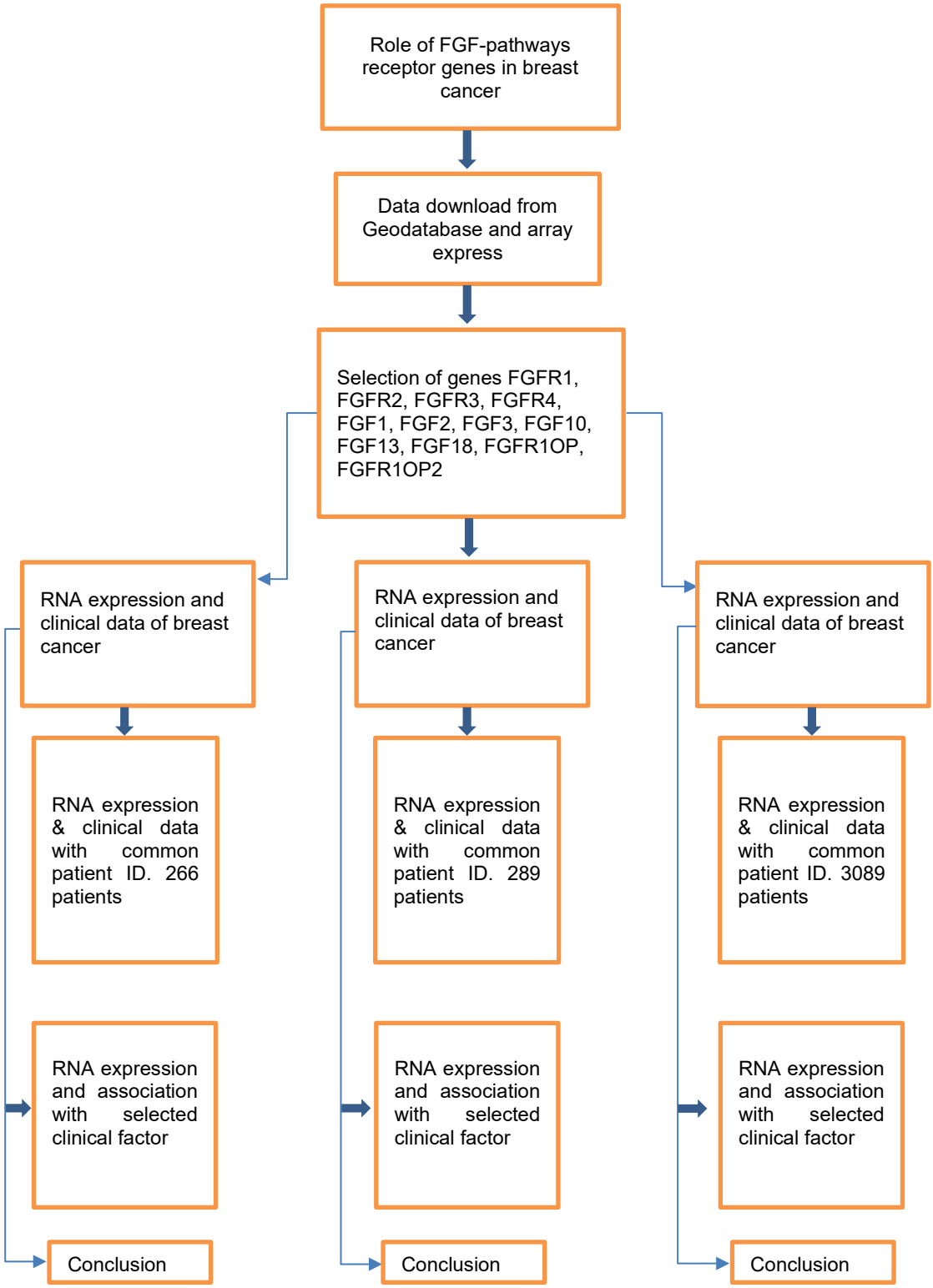
This study aims to predict the binding interaction and to explore the binding mode of polyphenol compounds from *A. occidentale* with α-glucosidase and Dipeptidyl peptidase-4 inhibitor enzymes by using molecular docking simulation technique. Here, the interactions between the polyphenol compounds from *A. occidentale* with α-glucosidase and Dipeptidyl peptidase-4 inhibitor enzymes were assessed by evaluating the binding energy, the formation of the hydrogen bond, electrostatics and hydrophobics with the active site residues of both target proteins. The study improves understanding of the ligand interaction with the target proteins, in which it provides the potential binding modes and binding interaction which could be further exploited computationally and experimentally as the potential inhibitor for diabetic enzymes of potential targets for future new anti-diabetic drug design. FGFRs are transmembrane proteins that contain intracellular tyrosine kinase domains, an acid box, and external immunoglobin-like (Ig) domains [26]. Heparan sulfate proteoglycans (HSPGs) enhance the binding of fibroblast growth factors (FGF) to FGFs, which commence the activation process [27]. FGF stimulate signaling in the tumor micro-environment by acting on neighbouring cells (paracrine) or on the same cell (autocrine) [28]. Multiple downstream signalling cascades are triggered when FGFs bind to FGFRs, causing receptor dimerisation and intracellular tyrosine residue autophosphorylation. [29]. One such pathway is the PI3/AKT pathway, which activates cell growth and survival and is mediated by FRS2, GAB1, and PI3k [30]. Another crucial pathway is the RAS/MAPK pathway, involving SOS, GRB2, RAS, RAF, MEK, and MAPK, which support cell division and proliferation [31]. Additionally, activation of PLCγ cause in the generation of IP3 and DAG, resulting in to calcium release and PKC activation [32]. The direct stimulation of STAT proteins, which proceed into the nucleus and substitute the expression of certain genes [33]. In cancer cells, mutations, gene amplification, translocations, and abnormal expression of FGFs and FGFRs result in uncontrolled cell proliferation, survival, migration, invasion, and angiogenesis [34]. The tumor stroma can contribute additional FGFs, enhancing paracrine signaling and further stimulate tumor growth [35]. Therefore, cumulative outcome of these signaling cascades enhanced cell proliferation, differentiation, migration, invasion, and angiogenesis are critical for cancer initiation and progression shown in Figure.1 [36].

In the similar vein, microRNAs (miRNAs), a class of tiny non-coding RNAs that target mRNAs to regulate gene expression, can likewise be highly influential in cancer [37]. Their abnormal expression is implicated in various human diseases, including cancer [38]. For example, abnormal expression of miRNA has been reported in human chronic lymphocytic leukemia, a malignancy that affects the tissues that make blood, where miRNA impression was associated with particular clinicobiological features [39]. Additionally, human breast cancer has abnormal expression of miRNAs when compared to normal breast cancer tissues [40]. Overall miRNA expression clearly separates malignant from normal tissues, mir-125b, mir-145, mir-155, and mir-21 are the most significantly disturbed miRNAs [41]. Moreover, we could examine miRNAs whose expression corresponded with particular biopathologic characteristics of breast cancer, like the expression of progesterone and estrogen receptor, tumor stage, vascular invasion, or proliferation index [42].

Survival analysis examines the time until one or more events occur, such as death in biological organisms [43]. In breast cancer survival studies using the SEER Program, survival rates vary based on tumor size and lymph node status. Larger tumors and positive lymph node involvement correlate with decreased survival rates. The study suggests, lymph node status act as guage of the tumor's potential for metastasis, rather than disease development to remote locations [44]. The recurrence of Breast cancer, defined as the reappearance of cancer cells after remission, can occur at any time, with most recurrences happening within the first three to five years after primary treatment. Recurrences may be local (in the treated breast) or distant (in other parts of the body). The timing of recurrence is not indicative of incorrect treatment but rather small surviving cancer cell populations that become detectable over time [45].

Materials and Methods

Study Design



Data Sets

Datasets with comprehensive RNA expression and clinical breast cancer information were obtained from the Geo Database [46]. The Geo Database used to store Geographic Information System (GIS) in a single large file [47], which has multiple data containing polygon, and polyline layers. It has a common way of organizing data than different shape file in multiple folders [48]. For each cancer type, only those samples were extracted for the analysis which have RNA expression and clinical feature information [49]. RNA expression z-score value greater than 1 was considered up-regulated and less than 1 was considered down-regulated [50].

Out of a total of 2303 samples, 266 patient samples are available in the first dataset, 289 patient samples are available in the second dataset, and 2089 patient samples are available in the third dataset. Table 1 displays the clinicopathological characteristics of the first dataset of breast cancer, Table 2 presents the clinicopathological characteristics of the second dataset, and Table 3 displays the clinicopathological.

Table 1. Clinicopathological features of 266 breast cancer patients

Characteristics	No.	Percentage
Age		
>50	97	36.47%
<=50	168	63.16%
NA	1	0.38%
Organism		
Homo-sapiens	266	100%
Sex		
Female	266	100%
Male	0	0%
T-stage		
T1	59	22.18%
T2	126	47.37%
T3	68	25.56%
NA	13	4.89%
GRADE		
G1	45	16.92%
G2	89	33.46%
G3	125	46.99%
NA	7	2.63%

Table 2. Clinicopathological features of 289 breast cancer patients

Characteristics	No.	Percentage
Age		
>50	48	2.63%
<=50	202	69.9%
NA	39	13.49%
Organism		
Homo-sapiens	289	100%
Sex		
Female	289	100%
Male	0	0%
Lymph Node Status		
Negative	159	55.02%
Positive	81	28.03%
NA	49	16.96%
TumorSize		
>2.9	212	73.36%
<=3	39	13.49%
NA		
GRADE		
G1	68	23.53%
G2	166	57.44%
G3,G4	55	19.03%
Vital Status		
Alive		
Dead	89	30.8%
NA	200	69.2%
EstrogenReceptorStatus		
Positive	211	73.01%
Negative	34	11.76%
Unknown	4	1.38%
NA	40	13.84%

Table 3. Clinicopathological features of 2089 breast cancer patients

Characteristics	No.	Percentage
AGE		
>50	429	20.54%
<=50	575	27.53%
NA	1298	62.13%
SEX		
Male		
Female	2089	100%
VITAL STATUS		
Alive	474(0)	22.69%
Dead	159(1)	7.61%
NA	1669	79.89%
T-STAGE		
T1	177	8.47%
T2	397	19%
T3	126	6.03%
NA	1388	66.44%
ESTROGEN RECEPTOR		
Positive	733	35.09%
Negative	421	20.15%
NA	934	44.71%
PROGESTERONE RECEPTOR		
Positive	394	18.86%
Negative	418	20.01%
NA	1276	61.08%
HER2		
Positive	190	9.1%
Negative	682	32.65%
NA	1216	58.21%
LYMPH NODE		
Positive	354	16.95%
Negative	406	19.44%
NA	1328	63.5%
KI67 IHC		
Positive	144	6.89%
Negative	58	2.78%
NA	1886	90.28%
GRAGES		
G1	90	4.31%
G2	235	11.25%
G3	623	29.82%
NA	938	44.9%
DFS STATUS		
Negative	169	8.09%
Positive	83	3.97%
NA	1836	87.9%
OVERALL SURVIVAL		
Positive	159	7.61%
Negative	474	22.69%
NA	1455	69.65%

BRB-Array Tool

A combined programme for the statistical analysis and visualization of microarray gene expression, methylation, copy number and RNA-Sequence knowledge data is the BRB-array tool [51]. It had been developed proficient statisticians, it contributed to the advancement of enhanced techniques for the planning and evaluation of microarray-based research. The visual and analytical imaging tools are added to Excel as an add-in. [52]. The robust R statistical (applied math system) is used to construct the analytical and visualization tools themselves [53], in C and Fortran programs and in Java applications [54]. The component that unifies the pieces and conceals from the user the complexity of the analytical techniques is Visual Basic for Applications. A variety of potent analytical and visual picture tools designed especially for microarray knowledge analysis are integrated into the system [55].

Descriptive File

After importing the data file into an Excel sheet, the sheet comprises four different tabs with various types of data. The initial tab contains the descriptive file, essential for extracting crucial information from the clinical data file. The descriptive file should include details such as patient survival time, status (deceased or alive), DFS (Disease-Free Survival) events, metastasis, T-stage, and Grade. This information is necessary to derive output results pertaining to our gene of interest, which serves as the target genes for the analysis of their functionality in breast cancer—determining whether they are up-regulated or down-regulated [56].

Class Comparison

Once the descriptor file was finalized, the class comparison between groups of arrays commenced to analyze critical information such as, DFS events, age, T-Stage, Grade, and survival time. This comparison aims to obtain output results for each set of data. The output result will include various genes, among which our main target genes are FGF1, FGF2, FGF3, and FGF4. Identifying these genes involves extracting the gene names and their associated classes with different values. The analysis then notes whether each gene is up-regulated or down-regulated in the two distinct classes [57].

Statistical Analysis

IBM SPSS Statistics was the statistical tool used for all of the tests. In this tool we performed Pearson Correlation test, which is used to measure the strength and direction of the linear relationship between two continuous variables. It might be useful in your investigation to ascertain whether two variables. For example, patient outcomes and gene expression levels having a statistically significant relationship. Strong relationships are shown by correlation coefficients near 1 or -1, but little or no linear relationships are suggested by values near 0. Whereas, Fisher's test is used to evaluate the relationship between two category variables. It is frequently employed to ascertain whether the variables in a contingency table exhibit nonrandom connections. Fisher's test may be helpful in this situation to investigate the association between categorical gene mutations and the prognosis or outcomes of breast cancer (also categorical). and Kaplan Meier is used to estimate the time until an event, such death or a cancer recurrence, occurs. Kaplan-Meier analysis was used in your study to evaluate disease-free survival (DFS) and overall survival (OS) across various patient groups. Researchers can evaluate the effects of different factors on survival outcomes and compare survival durations between groups (such as patients with and without particular gene mutations) using the survival curves produced by Kaplan-Meier analysis. P-values less than 0.05 were deemed statistically significant in your study, meaning that there is less than a 5% chance that the observed results were the result of pure chance, implying a significant link or difference [58].

Results

Overall and Disease-Free Survival

Association of Genes with Overall Survival (OS)

We further investigated the association of genes RNA expression with overall survival (OS) and disease-free survival (DFS). According to Kaplan Meier plots, FGFR1OP2 amplification was associated with poor survival Figure 2, FGFR2 amplification was associated with good survival Figure 3 and FGF2 amplification was associated with poor survival in breast cancer Figure 4.

Association of Genes with Disease Free Survival (DFS)

A single gene connection was found to be associated with disease-free survival in breast cancer when the evaluation of disease-free survival was also conducted. Amplification of FGFR1OP2 was associated with poor disease-free survival (DFS) in patients with breast cancer, as seen by Kaplan Meier plots Figure 5.

Overall Association of FGF Genes in Different RNA Expression Data

The class comparison between groups of arrays has began to compare important information such as DFS event, age analysis, T-Stage, Grade, and survival time to get the output result for each dataset. The output will include different genes, among which are the genes of interest: FGF1, FGF2, FGF3, and FGF4. By identifying these genes, the gene names are extracted along with classes having different values. From those value, it is noted which genes are upregulated or downregulated in two different classes. Several associations were observed in RNA expression with clinicopathological features. In breast cancer, FGFR1 was associated with early-stage of grades, whereas FGFR1OP was associated with late-stage grades across different datasets. In terms of expression, FGFR1 was associated with ER-positive and PR-positive status; FGFR2 was associated with ki67 IHC-negative status; FGFR3 was associated with ER-positive, PR-positive and lymph node-positive status; and also HER2-negative and ki67 IHC-negative, FGFR4 was associated with HER2-negative; FGF1 was associated with ER-positive and PR-positive status; FGF2 was associated with ER-negative, PR-negative, HER2-negative and lymph node-negative, FGF3 was associated with ER-positive, PR-positive, lymph-node positive, HER2-nagative, and ki67 IHC-negative Status; FGF10 was associated with ER-positive, FGF13 was associated with ER-positive, PR-positive, lymph-node positive, HER2-negative, and Ki67 IHC-negative; FGF18 was associated with ER-positive and ki67 IHC-negative; and FGFR1OP2 was associated with HER2-negative (referenced in Table 4).

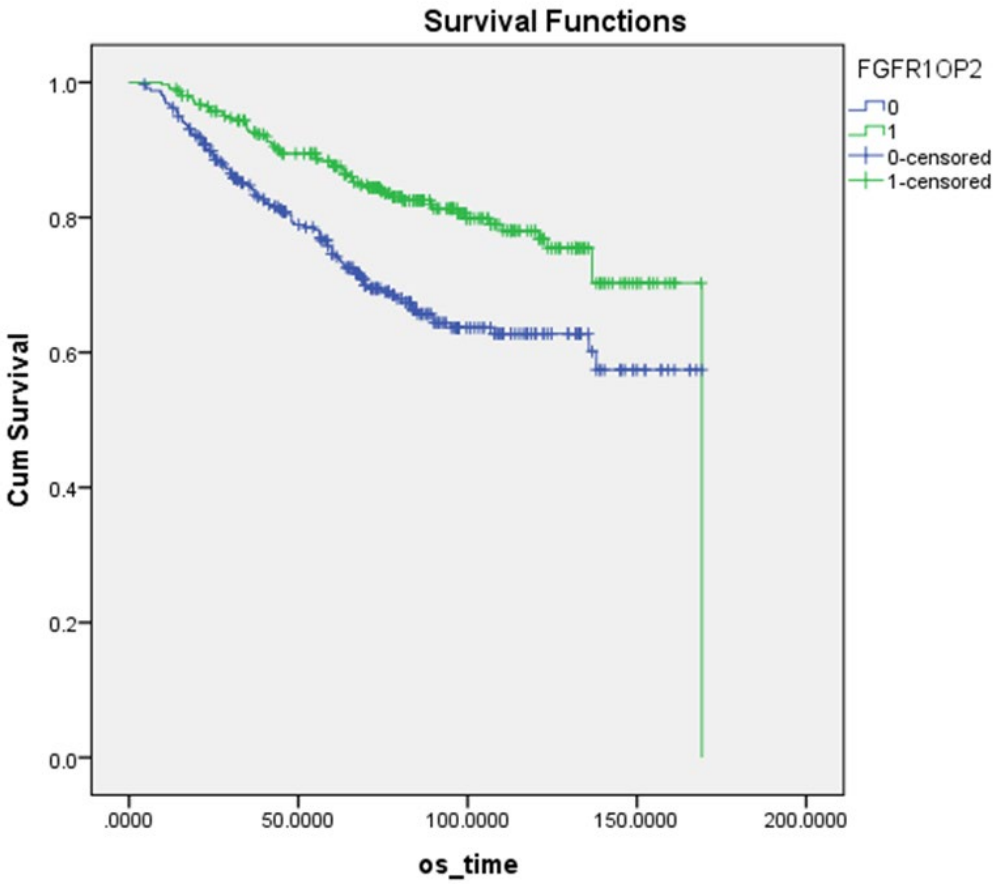


Figure 2. Association of FGFR1OP2 gene with overall survival in breast cancer in RNA expression

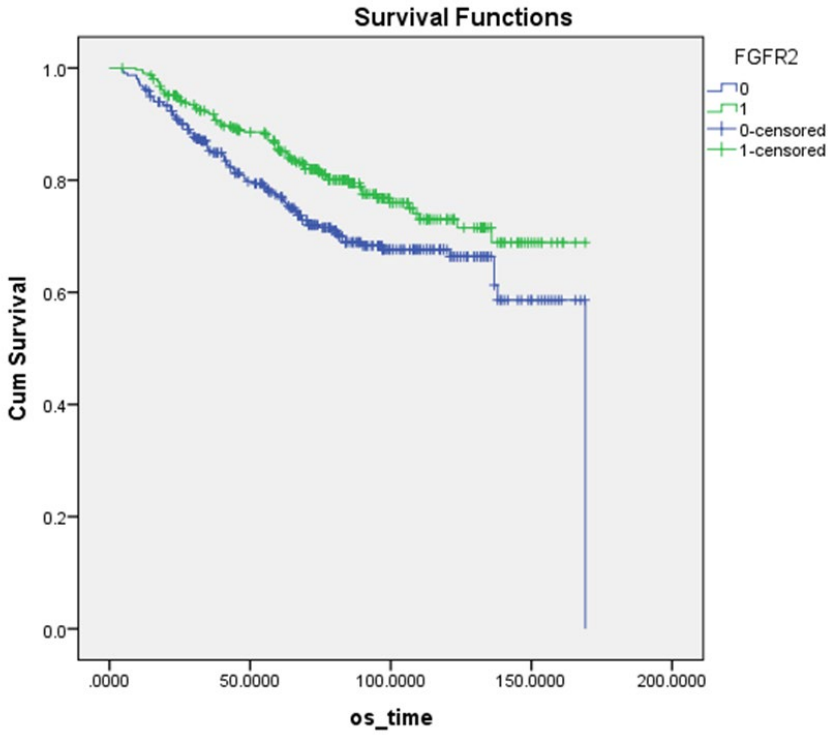


Figure 3. Association of FGFR2 gene with overall survival in breast cancer in RNA expression

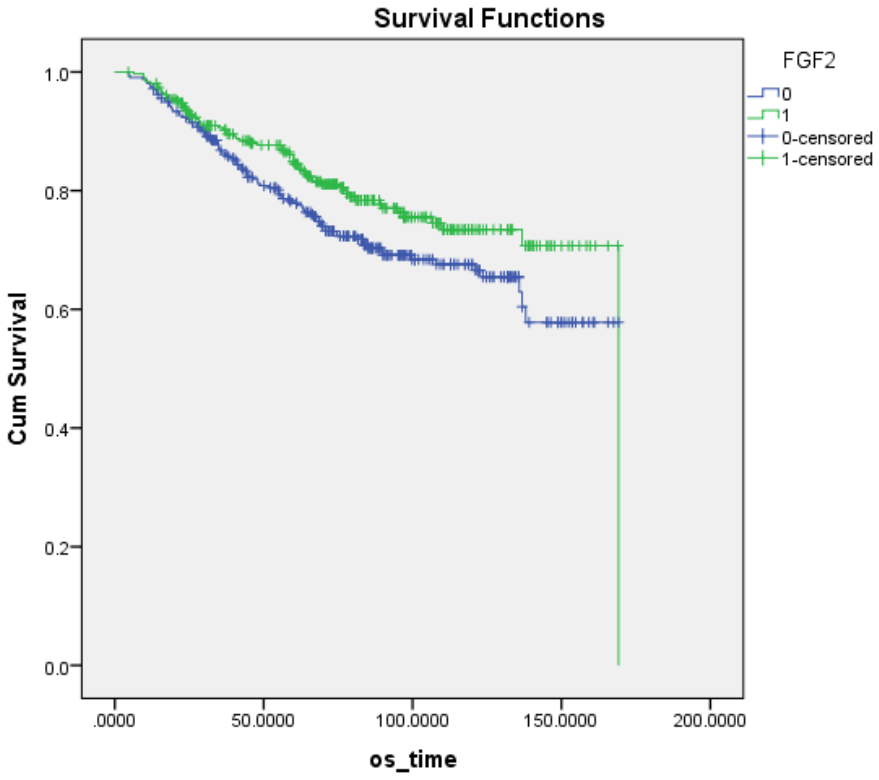


Figure 4. Association of FGF2 gene with overall survival in breast cancer in RNA expression

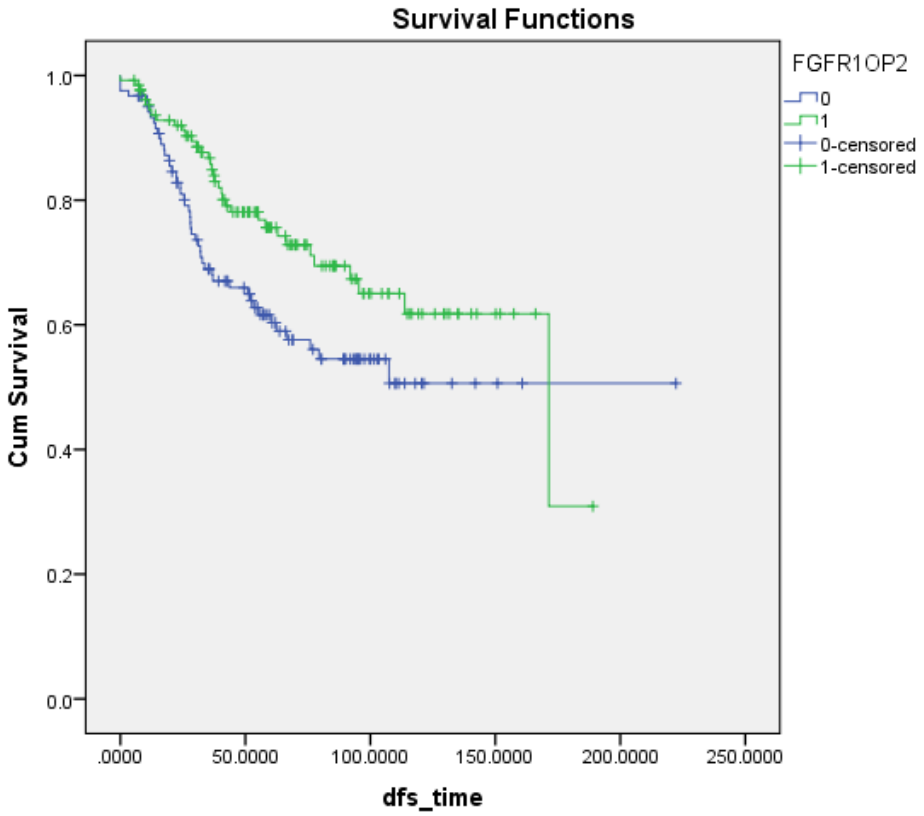


Figure 5. Association of FGFR1OP2 gene with disease-free survival in breast cancer in RNA expression

Table 4. Overall association of FGF genes in different RNA expression data

Gene	Data Set 1		Data Set 2		Data Set 3	
	Grade	T-Stage	Grade	T-Stage	Grade	T-Stage
FGFR1	Up-regulated in G2	Up-regulated in T2	Up-regulated in G1, G2		Up-regulated in G2, G3	
FGFR2			Up-regulated in G1, G2		Up-regulated in G2, G3	Up-regulated in T2, T3, T4
FGFR3	Up-regulated in G1				Up-regulated in G2, G3	
FGFR4			Up-regulated in G2, G3			Up-regulated in T1, T2
FGF1		Up-regulated in T1			Up-regulated in G2, G3	Up-regulated in T2, T3, T4
FGF2					Up-regulated in G3	Up-regulated in T2, T3, T4
FGF3	Up-regulated in G1					Up-regulated in T1
FGF13			Up-regulated in G1, G2			
FGF18	Up-regulated in G1	Up-regulated in T1			Up-regulated in G3	
FGFR1OP	Up-regulated in G3				UP-regulated in G2, G3	Up-regulated in T2, T3, T4
FGFR1OP2	Up-regulated in G2					Up-regulated in T2, T3, T4

Discussion and Conclusion

Cancer formation in breast tissue is driven by the uncontrolled proliferation of normal cells, marking the initial stage of cancer development [59]. Tumors can be categorized as benign, often not life-threatening, or malignant, which have the potential to become harmful [60]. Malignant tumors have the ability to metastasize, or spread through the bloodstream, whereas benign tumors do not [61]. Stage IV breast cancer is considered advanced and is typically characterized by metastasis to other organs [62].

Fibroblast growth factors (FGFs) and fibroblast growth factor receptors (FGFRs) influence a variety of physiological processes, including angiogenesis regulation, wound healing, and embryonic development [39]. The FGF/FGFR signaling network plays a critical role in cancer cell proliferation, survival, differentiation, migration, and apoptosis [63]. Disruption of the FGF/FGFR pathway has been closely linked to various cancers and developmental disorders due to these roles [64]. This study aimed to determine whether genes in the FGFR pathway have general roles in cancer or specific roles in particular cancer types. Our research showed that FGFR pathway genes exhibit distinct behaviour across different breast cancer RNA expression datasets. Additionally, studies suggest that FGFR mutations are associated with an increased risk of breast cancer development and progression [65]. Our findings offer important insights into the role of FGFR genes in breast cancer.

Notably, FGFR1OP2 was identified as an oncogene associated with poor prognosis in breast cancer, with its over-expression linked to reduced overall survival. Research has shown that FGFR1OP2 can act as both an oncogene and a tumor suppressor in specific cellular contexts [66]. FGFR2, a novel gene linked to myeloproliferative syndrome, has been shown to function as a tumor suppressor in breast cancer, with overexpression associated with favourable overall survival [67]. Similar to FGFR1OP2, FGF2 is associated with poor prognosis, exhibiting amplification linked to reduced survival [68]. FGF2 signaling in primary tumors has been associated with lower recurrence-free survival (RFS), regardless of age, grade, stage, or FGFR amplification status. In the same study, FGF2 pathway activity was predictive of anti-estrogen resistance and shorter RFS in three datasets, as well as shorter overall survival (OS) in a fourth dataset. Analyses of large datasets with clinical annotations revealed that FGF2 pathway activity predicts RFS regardless of factors such as age, tumor grade, stage, and gene amplification status [69].

Furthermore, studies support our finding that FGFR1OP2 functions as an oncogene in breast cancer, with its overexpression linked to disease-free survival [70]. Large dataset analyses indicate that FGF2 pathway activity predicts RFS across diverse clinical variables, confirming our conclusion that FGFR1OP2 acts as an oncogene in breast cancer, with overexpression associated with disease-free survival [71].

Additionally, FGFR1 has been linked to poor prognosis and was found to be up-regulated in early-stage tumors across several datasets, indicating a role in early cancer cell proliferation [72]. As receptors for fibroblast growth factors, FGFR1 regulates cell migration, differentiation, survival, and proliferation during development and in adulthood [73]. Similarly, multiple datasets showed that FGFR1OP is up-regulated in late-stage breast cancer [74]. Our study suggests that FGFR genes may function as both oncogenes and tumor suppressors in breast cancer. Given these contrasting roles, further investigation is essential to gain a comprehensive understanding of the tumor-suppressive properties of FGF pathway genes.

Conflicts of Interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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