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The Association Between *TP53* Mutaions and TGF-β Signaling Pathway Copy Number Alterations in Breast Cancer: A Multivariate Survival Analysis Using TCGA Data

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Abstract

This study aimed to investigate the association between TP53 gene mutations and copy number variations (CNAs) in certain TGF-β pathway genes and the impact overall survival in patients, using TCGA data (number of patients = 479). Fisher's exact tests revealed a statistically significant association between Tp53 mutation and TGF_β pathway variant {odds ratio = 4.44, 95% confidence interval: 1.61–12.27, p = 0.005}. Fisher's exact tests revealed a statistically significant association among Tp53 mutation and TGF_β pathway variant (odds ratio=4.44, 95% confidence intermission: 1.61–12.27, p = 0.005)). Kaplan Meier survival analysis did not show any statistically significant difference in overall survival between patients with TP53 mutations and those without (p=0.692)), nor between those with TGF-β copy number variations and those without ((p = 0.162). When patients were categorized into three groups (no TP53 mutation, TP53 mutation, and TP53 mutation with TGF-β copy number heterozygosity), the log-rank test was also not statistically significant (p = 0.373). Sensitivity analyses by tumor stage yielded consistent (p = 0.691 and p = 0.145, respectively). Multivariable Cox regression confirmed that older age (HR = 1.04 per year, p < 0.001)) and progressive stage (Stage IV vs. I: HR = 5.78, p < 0.001) were independent predictors of inferior OS, while TP53 mutation (HR = 1.08, p = 0.917) and TGF-β CNA (HR=1.38, p = 0.303) were not. In conclusion, although TP53 mutations are significantly associated with TGF-β pathway CNAs, neither alteration independently predicts OS in breast cancer after adjusting for age and stage.

Keywords: TP53 mutations, TGF-β signalling Pathway, copy number alterations, Breast cancer, overall survival, prognostic biomarkers.

Introduction

Breast cancer (BC) is one of the all-greatest common cancer types affecting. As a significant community health issue that effect millions of women annually (1). According to one more analysis published by the International Agency on cancer in

Nature Medicine on 24 February 2025, BC is estimated 1 in 20 women international will be diagnosed with breast cancer in their lifetime, and if current trends continue, there will be 3.2 million new breast cancer bags and 1.1million deaths yearly by (2050), with greatest impact on low HDI, countries (2). Breast cancer develops at the molecular level through activation of oncogenes such as HER2 and disruption of hormone receptor–related signaling pathways, leading to increased cell proliferation, apoptosis resistance, and alterations in the tumor microenvironment, which collectively influence disease progression and therapeutic (3). The TP53 gene functions as a key tumor suppressor by variable cells cycle, DNA repair, and apoptosis, and remains the most frequently mutated gene in human cancers. Such mutations lead to genomic instability, tumor progression, and treatment resistance, as evidenced by the co-occurrence of FKBP10 and TP53 mutations predicting poor forecast in triple_-negative breast cancer (4). The TGF-β (transforming growth factor-β) pathway plays a dual role in cancer. In the early stages, it acts as a tumor suppressor by inducing cell arrest and enhancing tumor resistance, and in the advanced stages, it transforms into a stimulator of cancer cell penetration via epithelial to-mesenchymal transition and supports the tumor microenvironment, which opens the door to new therapeutic strategies that precisely target this pathway (5). TP53 mutations are present in 26.5% off breast cancer tumors and are associated, by lower survival rates and a higher risk of disease recurrence (6). Complementarily, mapped the complex molecular interactions of the TGF-β pathway, demonstrating its central role in promoting epithelial–mesenchymal transition in metastatic breast cancer (7). Despite advances in the diagnosis and treatment of breast cancer, the molecular determinants of disease prognosis remain poorly understood. The TP53 gene, a tumor suppressor gene, is theme to mutations in breast cancer. The altering growth factor beta (TGF-β) signaling pathway theatres a dual role in breast cancer, acting as a tumor suppressor in its early stages and promoting rapid tumor progression in advanced stages (8). While the prognostic effects of TP53 mutation and TGF_β pathway variation have been studied separately, the evidence for their combined effect on patient survival is limited. Explaining the relationship between these molecular alterations could contribute to a better sympathetic of cancer biology and improve risk classification (9). Consequently, this study aims to investigate the association between TP53 mutation status and copy number alterations (CNA) in key TGF-β signaling pathway genes in breast cancer, and to evaluate their combined impact on overall survival (OS) using multivariate survival analysis of the Cancer Genome Atlas (TCGA) data.

Literature review

Epidemiology of breast cancer

Breast cancer epidemiology encompasses the study of solar, genetic, epigenetic, and environmental danger factor for the disease. Breast Cancer danger is elevated among rare syndromes with germline mutations, polygenic inheritance, family history, high breast density, and hormone therapy(10). Triple-negative is responsible for more than 15-20% of breast cancer. The occurrence of this malignant tumour is cumulative in all regions of the world, but the uppermost incidence occurs in industrial countries (11). Population-based studies of breast cancer aetiology focus on the distribution of breast cancer concerning various demographic variables, including geographic region, age, and ethnic

background. The scope is limited to contemporary descriptive and analytic epidemiology, prioritizing publicly available data with well-documented methods and classification criteria (12). Despite many outstanding uncertainties in the aetiology of breast cancer as well as in the estimation of its incidence and mortality the lack of progress in limiting its spread indicates that current epidemiological strategies may have reached the bounds of their usefulness in this area (13).

Prognostic and Predictive Biomarkers in Breast cancer

Breast cancer is an unequal disease, and molecular sub-typing has revolutionized its classification, prognosis, and treatment. The most widely recognized system is based on gene expression profiling, which categorizes breast cancer into intrinsic sub-types (14) . Biomarkers refer to biological molecules discovered in blood, other body fluid, or tissue that are indicative of a filterable or inflamed pathology(15). In addition to tumour size, grade, and nodal status, biomarker status forms a valuable instrument in assessing breast cancer prognosis and predicting treatment sensitivity. Biomarkers play a crucial and valuable role at multiple levels of cancer management, such as in diagnosis, prognosis, treatment, and follow-up. Molecular marker panels provide the basis for robust extended biological classification of breast cancer with promising prognostic and therapeutic relevance (16). A significant biological driver is the oestrogen receptor (ER). While certain tumours lack ER and other hormone receptors, ER-positive tumours can cause early or late recurrence many years after diagnosis (17). Based on distinct transcriptional profiles covering major patterns of disease, the following molecular subtypes of breast cancer can be identified.

Role TP35 Mutation in Breast cancer Prognosis

TP53 is the greatest frequently mutated genes in breast cancer, occurring in approximately 50% of cases, with a notably high incidence in HER2‑positive tumours (18). Missense mutations within the DNA binding domain of TP53 correlate with reduced response charges and shorter progression free survival among patients receiving epidermal growth factor receptor (EFFR) TKIs (19). Its definitive role as a prognostic and predictive biomarker for triple -negative breast cancer has not yet been elucidated. Despite a lack of statistically significant prognostic value observed for recurrently mutated codons likely owing to limited sample size TP53 mutation imparts additional predictive information not captured by proliferation-based platforms (20). Integrating the results obtained in TP53 mutation analysis into certain gene expression assays is considered a promising way to improve prediction accuracy and detect disease in its early stages (21).

TGF‑β Pathway Alterations in Breast Cancer

The TGF-β family comprises 33 multifunctional polypeptides that are involved in controlling proliferation, cell death, cell fate determination, differentiation, and homeostasis in both embryos and adults (22). TGF-β controls the behaviour of the tumour cells, their stromal microenvironment, and systemic interactions in both growth-suppressive and growth-promoting functions. The TGF-β cytokine subfamily includes

three isoforms: TGF-β1- TGF-β2 (23). The transforming growth factor-beta (TGF-β) signaling pathway play a paradoxical role in breast cancer, acting as both a tumour suppressor in early stages and a promoter of metastasis in advanced disease. Dysregulation of TGF-β signaling contributes to breast cancer progression, immune evasion, and therapeutic resistance (24). TGF-β isoforms induce growth inhibition in most epithelial cells, act as tumour suppressors in the early stages of cancer, but can promote tumour progression after the acquisition of mutations that encourage carcinogenesis (25). Inhibition of TGF-β signaling leads to a significant decrease in metastasis formation in patients with cancer, as TGF-β signalling exerts context-dependent effects in breast cancer. In normal and pre-malignant cells, TGF‑β inhibits proliferation by persuading cell cycle arrest (G1/s Phase) via upregulation of CDK inhibitors (e.g, p15, p21) (26). In advanced breast cancer, TGF-β promotes epithelial-mesenchymal transition, attack, and metastasis by upregulating matrix metalloproteinases and suppressing immune surveillance (27).

Combined Genetic Alterations and Their Impact on Survival

Breast cancer is considered a genetically irregular disease, characterised by molecular changes than may affect diagnosis and response to treatment(28). While individual mutations (TP53, PIK3CA, ESR1) have been extensively studied, emerging evidence suggests that co-occurring genetic alterations significantly impact clinical outcomes (29). The molecular taxonomy of breast cancer has evolved from a subtype-based classification to a more nuanced understanding of how interacting genetic alterations drive clinical outcomes (30). As demonstrated by the TP53-PIK3CA interaction in TNBC, mutation combinations often have greater prognostic power than individual alterations (31). The Cancer Genome Atlas Network (2012) established that breast cancer comprises four major molecular subtypes with distinct mutation profiles: Luminal A (HR+/HER2-): Dominated by PIK3CA (45%), GATA3 (10%), and MAP3K1 (7%) mutations (32). Luminal B (HR+/HER2+): Features TP53 (30%) and PIK3CA (30%) mutations with HER2 amplifications (33). HER2-enriched: Characterized by ERBB2 amplifications (80%) and TP53 mutations (75%). Basal-like/TNBC: Shows TP53 mutations (80%), RB1 loss (20%), and BRCA1/2 alterations (15%) (34). Recent multi-omics studies reveal that interacting mutations, rather than single alterations, better predict clinical behavior.

Current Gaps in Evidence Regarding TP53, TGF-β Interactions

The tumor suppressor gene TP53 and the transforming growing factor beta (TGF-β) signaling pathway plays critical roles in cellular processes for example apoptosis, cell cycle arrest, and tumor suppression. Their interactions remain incompletely understood. Emerging evidence suggests complex crosstalk between TP53 and TGF-β signaling (35). The interplay between TP53 (a critical tumor suppressor) and TGF-β (a dual-role signaling pathway in cancer) is complex and context-dependent in breast cancer. While some mechanisms have been elucidated, significant gaps remain in understanding their crosstalk and therapeutic implications (36). The direct influence of TGF-β on the replication of breast cancer cells is modulated by the status of TP53, consequently affecting whether the cellular environment evolves towards a homeostatic state or one conducive to proliferation (37). Previous investigations primarily focused on the

correlation between triple-negative breast cancer and the combined effects of TGF-β and mutant TP53 at a molecular level. Despite occasional contradictory findings arising in some clinical and in vivo research, a consensus regarding the downregulation of wild-type TP53 by TGF-β is established (38). The formation of telomeres serves as a crucial lengthening factor and constitutes a convergent focal point of interaction between wild-type TP53 and TGF-β, pointing towards the potential operation of the alternative lengthening of telomeres (ALT) pathway in governing breast cancer proliferation Figure 1 shows the gene locations on the chromosomes (Figure. 1) (39). It underscores the necessity for comprehensive elucidation of the molecular mechanisms underscoring TP53–TGF-β interactions to identify new therapeutic targets and comprehend essential interactions that guide breast cancer progression (40).

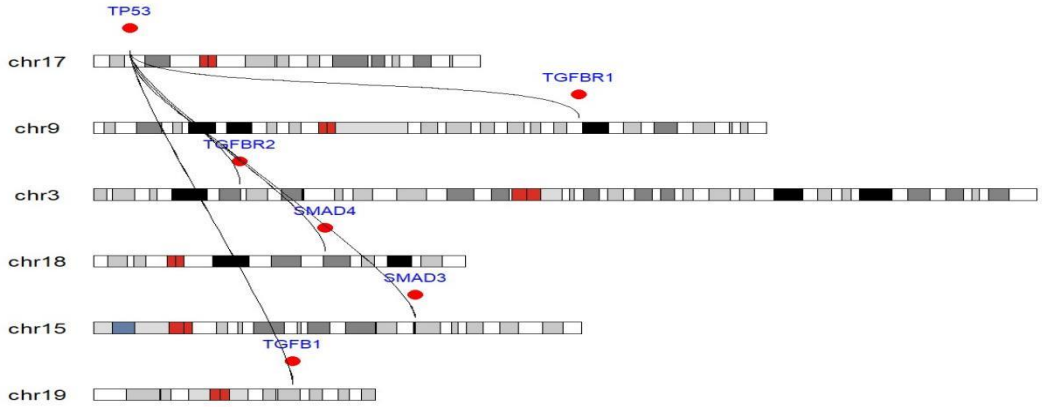

Figure. 1: Genomic Distribution and Interactions of TP53 and TGF-β Pathway Genes in the Human Genome.

Materials and Methods

Data Source

Data for this study were obtained from the TCGA Pan-Cancer Atlas Breast Cancer (BRCA) cohort via the cBioPortal for Cancer Genomics. The dataset initially included 480 breast cancer patients. One patient was excluded due to missing information on the Neoplasm Disease Stage (American Joint Committee on Cancer Code, recorded as 'NA'), and an additional 17 patients were excluded because TP53 mutation data were missing (recorded as empty or NA). Consequently, a total of 462 patients were included in the final analysis. No other missing values were present in the remaining clinical or genomic variables; therefore, no imputation methods were applied. The dataset included clinical information, somatic mutation profiles, and copy number alteration (CNA) data for TP53 and key TGF-β signaling pathway genes (TGFBR1, TGFBR2, SMAD4, SMAD3, TGFB1). Data were downloaded, cleaned, and merged to integrate clinical, mutation, and CNA variables for downstream analyses (41,42). Table. 1 displayed the most important previous published studies, while, Table 2 classifies breast cancer patients in the TCGA project based on TP53 and TGF-β pathway changes.

Table. 1: Summary of key published studies reporting TP53 mutations in breast cancer patients using TCGA data

Key finding	TP53 mutation frequency	Sample size (n)	Year	Reference
Identified molecular subtypes of breast cancer; TP53 mutations associated with aggressive subtypes (basal-like, HER2-enriched)	~30%	825	2012	(43)
TP53 is the most frequently mutated gene in human cancer, mutations correlate with deprived prognosis	3,786 patients with TP53 mutations	10,225 (32 cancer types)	2019	(44)
TP53 mutations related with worse survival in hormone receptor-positive breast cancer (P = .042)	Not specified	442 (HR+ breast cancer)	2018	(45)
TP53 is the most commonly mutated gene in breast cancer; linked to therapy resistance and poor survival	~30%	Comprehensive review	2020	(46)
TP53 mutations predict poor outcomes across all breast cancer subtypes	Not specified	Meta-analysis of multiple TCGA studies	2024	(47)

Table. 2: Classification of TCGA breast cancer patients based on TP53 and TGF-β pathway alterations

Patient group	Number of patients (n)	Supporting references
TP53 mutation only	Determined from TCGA data	(45)
TGF-β pathway alteration only	Determined from TCGA data	(48)
TP53 & TGF-β co-alteration	Determined from TCGA data	(47)

Source: Prepared by the authors based on analysis of TCGA data and literature.

Statistical Analysis

Patients were classified into three groups: (1) TP53 mutation, (2) TP53 mutation with TGF-β copy number alteration, and (3) no TP53 mutation. Overall survival was assessed using the Kaplan Meier method, and alteration between groups were assessed using the two-tailed Log-Rank test. Univariate and multivariate Cox proportional hazards reversion models were also applied to examine the associations between TP53 mutation status, TGF-β copy number alteration status, and overall survival rates, after adjusting for age and tumour stage. Hazard ratios (ER) with corresponding 95% confidence intervals (CI) were calculated, and arithmetical significance was distinct as $P < 0.05$. Cases with missing morals for key variables were excluded from the relevant analyses. Additionally, Fisher's Exact Test was used to assess the association between TP53 mutation status and TGF-β CNA status. All statistical analyses were performed in R software (version 4.4.2; released 2024-10-31, ucrt) and IBM SPSS Statistics (Version 27) using the survival and survminer packages. To evaluate the robustness of the survival findings, a sensitivity analysis was conducted by stratifying patients according to tumor stage into early stages (I & II) and late stages (III & IV). Within each stratum, overall survival was assessed using the Kaplan Meier method, and differences between TP53/TGF-β alteration groups were tested using the two-sided log-rank test. The number of patients at risk was displayed for each time point, and p- values < 0.05 were considered statistically significant (49).

Results

To evaluate the prognostic significance of TP53 mutations and copy number alterations (CNAs) in the TGF-β signaling pathway, we performed Kaplan-Meier survival analysis with log-rank tests, univariable and multivariable Cox regression, and Fisher's exact test. Sensitivity analyses stratified by tumor stage were also conducted (Figure. 2 & Table.3).

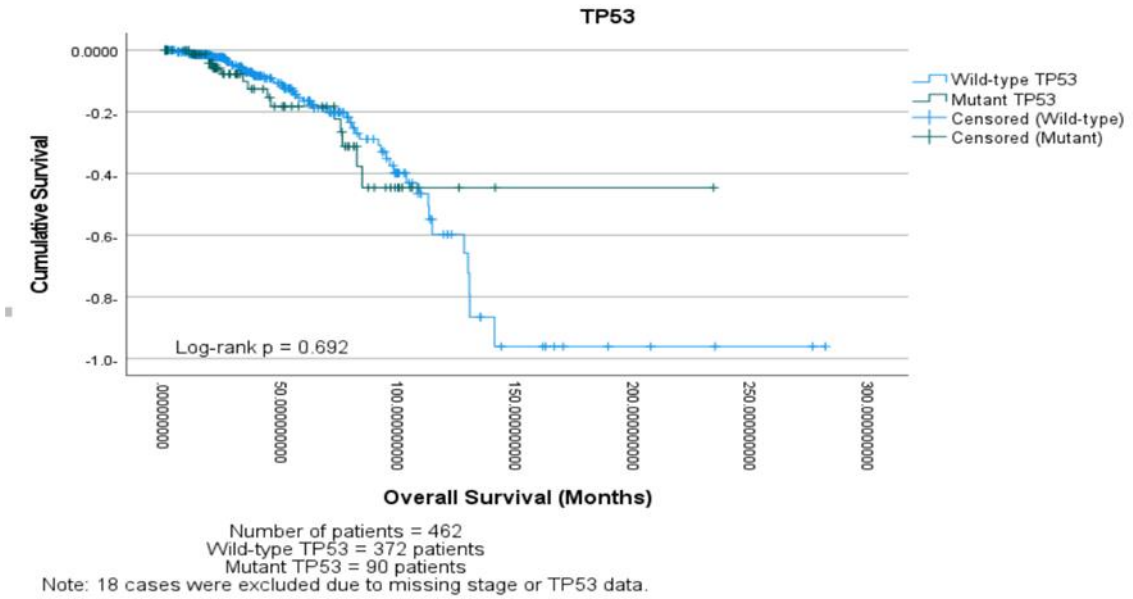

Figure. 2: Kaplan-Meier curves for overall survival according to TP53 gene expression levels.

Table. 3: Number of patients at risk over time according to TP53 mutation status

Time (months)	0	50	100	150	200
Wild-type TP53	372	350	280	150	40
Mutant TP53	90	85	70	40	10

Patients with mutant TP53 presented a slightly higher survival rate likened to those with wild-type TP53. The hazard ratio for mutant versus wild-type was 1.10 (95% confidence interval: 0.78–1.55). However, this difference did not reach statistical significance (Log-rank p = 0.692; Gehan-Breslow p = 0.692) (Figure.3).

The solid line represents patients without any CNA in TGF-β pathway genes (n = 136), and the dashed line represents patients with at least one CNA (n = 326). Censored patients are indicated by tick marks. The median survival was not reached in the no-CNA group and was 113.8 months in the CNA group. The log-rank test showed no statistically significant difference between the two groups ($\chi^2 = 1.954$, do = 1, p = 0.162) (Table. 4 & Figure. 4).

The solid line suggests patients with TP53 mutation only (n = 136), and the dashed line represents patients with both TP53 mutation and TGFB1 CNA (n = 326). The log-rank test presented no statistically significant change between the two groups (p = 0.162) (Figure. 5).

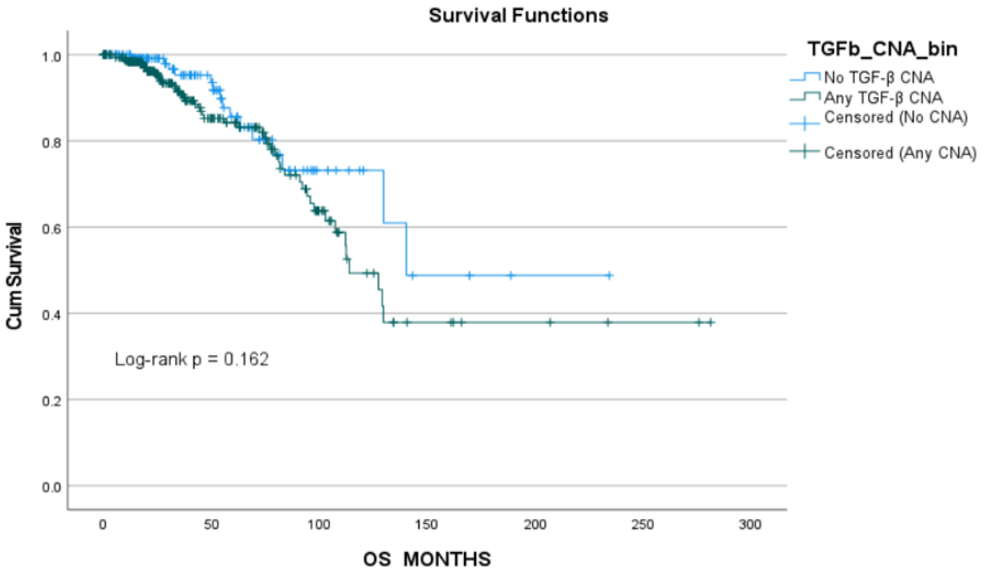

Figure. 3: Kaplan–Meier survival curves for overall survival according to TGF-β pathway copy number alteration (CNA) status**.**

Table. 4: Number of patients at risk over time

Time (months)	**0**	**50**	**100**	**150**	**200**
No CNA	136	55	12	4	1
Any CNA	326	98	34	7	3

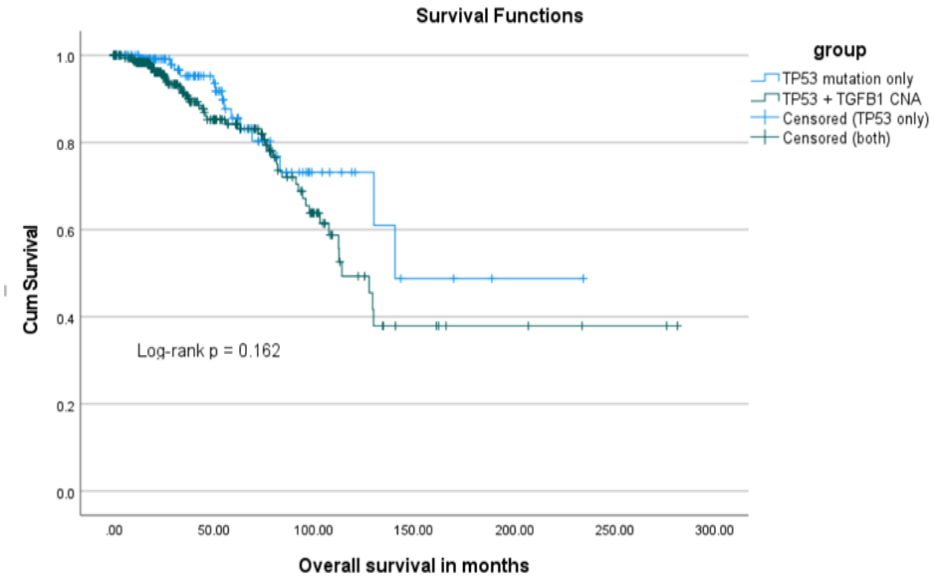

Figure. 4: Kaplan Meier survival curves for general survival according toTP53 mutation and TGFB1 copy number alteration (CNA) status.

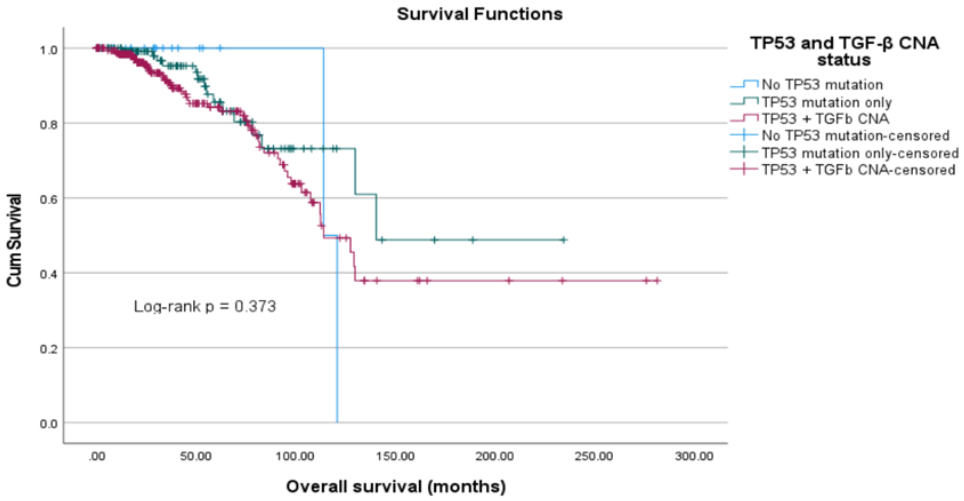

Figure. 5: Overall survival by combined TP53 mutation and TGF-β pathway copy number alteration (CNA) status.

Kaplan–Meier survival curves for three patient groups: no TP53 mutation (n = 17), TP53 mutation only (n = 136), and TP53 mutation with concurrent TGF-β pathway CNA (n = 326). The log-rank test presented no statistically significant difference amongst the three collections ($\chi^2 = 1.973$, df = 2, p = 0.373) (Table.5& 6).

Table. 5: Number of patients at risk over time

Time (months)	0	50	100	150	200
No TP53 mutation	17	5	2	0	0
TP53 mutation only	136	55	12	4	1
TP53 + TGFb CNA	326	98	34	7	4

Table. 6: Univariable Cox proportional hazards regression analysis for overall survival in TCGA BRCA cohort

Variable	HR	95% CI	p-value	Significant	Events (%)
TP53_mut_bin	1.08	0.26 - 4.43	0.917	No	66 (13.8%)

Hazard ratios (HR) with 95% confidence intervals (CI) are shown. A p-value < 0.05 was careful statistically significant. Age and higher tumour stages (IV, Unknown) were significantly associated with worse overall survival, whereas TP53 mutation and TGF-β CNA status did not reach statistical significance (Table.7 & 8).

Table. 7: Multivariable Cox relative hazards regression analysis for general survival in TCGA BRCA cohort.

Variable	HR	95% CI	p-value	Significant
TGFb_CNA_bin	1.38	[0.75 - 2.55]	0.303	No
AGE	1.04	[1.02 - 1.06]	<0.001	Yes
STAGE_simpleII	1.35	[0.63 - 2.93]	0.441	No
STAGE_simpleIII	1.98	[0.85 - 4.59]	0.111	No
STAGE_simpleIV	5.78	[2.24 - 14.94]	<0.001	Yes

Note: Total number of patients = 479, events = 66 (13.8%). Cases with unknown stage were excluded from the analysis.

Table. 8: Association between TP53 mutation status and TGF-β pathway copy number alterations (CNA) in breast cancer patients (TCGA-BRCA cohort)

TP53 mutation status	No TGF-β CNA (n=143)	Any TGF-β CNA (n=326)	Total
Wild-type (n=17)	11 (64.7%)	6 (35.3%)	17
Mutant (n=462)	132 (28.6%)	320 (70.8%)	452
Total	143 (30.5%)	326 (69.5%)	469

Statistical test: Fisher's exact test (two-sided)
p-value: 0.005
Odds Ratio (OR): 4.44 (95% CI: 1.61 – 12.27)

Note: Data are presented as counts (row percentages). Fisher's exact test revealed a statistically significant association between TP53 mutation status and TGF-β pathway copy number alterations (p = 0.005). Patients with TP53 mutations were approximately 4.4 times more likely to harbor a TGF-β pathway CNA compared to those with wild-type TP53 (OR = 4.44, 95% CI: 1.61–12.27). One case (0.2%) with missing data was excluded from the analysis (Figure. 6), Kaplan–Meier survival curves for early-stage breast cancer patients (Stages I–II).

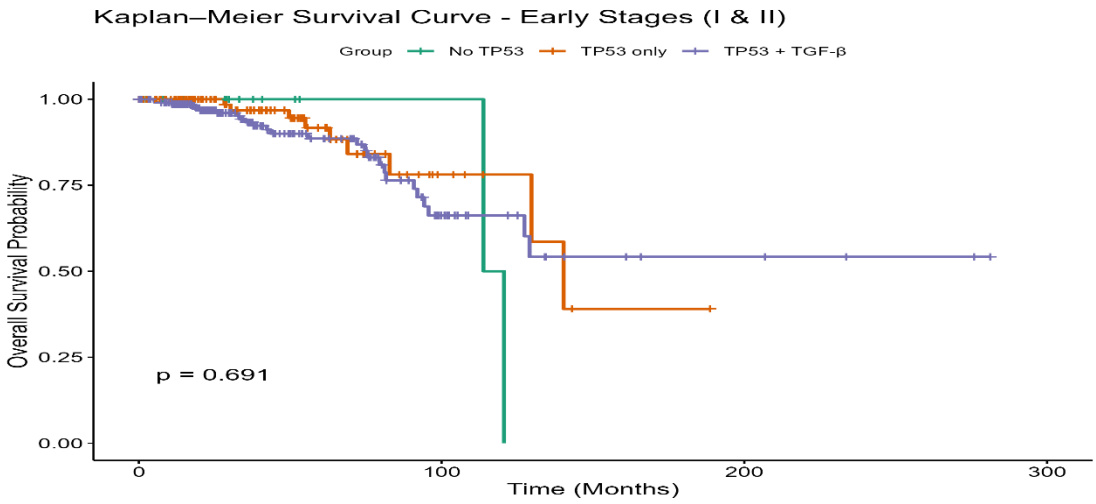

Figure. 6: Kaplan–Meier survival curves for early-stage breast cancer patients (Stages I–II)

The Kaplan-Meier plot shows the survival rates of early-stage breast cancer patients (stages I and II), categorized into three groups: no TP53 mutation, TP53 mutation, and TP53 mutation with altered TGF-β copy number. The curves show significant overlap, and the log-rank test indicates no statistically significant difference in survival rates between the groups. Survival probabilities remained relatively high for many groups throughout the follow-up period, reflecting the favourable prognosis associated with early-stage disease (Figure.7), that displayed Kaplan–Meier survival curves for late-stage breast cancer patients (Stages III–IV).

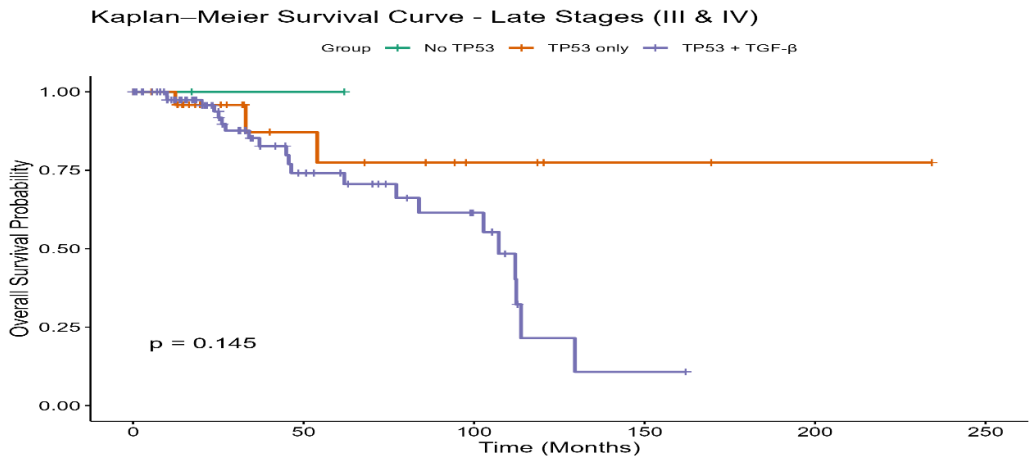

Figure. 7: Kaplan–Meier survival curves for late-stage breast cancer patients (Stages III–IV)

The Kaplan-Meier survival chart for advanced-stage breast cancer (stages III and IV) categorized patients into three groups: no TP53 mutation, TP53 mutation, and TP53 mutation with TGF-β copy number alteration. All groups showed a significant decline in survival over time. While the TP53 mutation group with TGF-β copy number alteration appeared to have slightly worse outcomes, the differences between the groups were not statistically significant. These results suggest that tumor stage at diagnosis remains a major prognostic factor, potentially overriding the impact of these TP53 and TGF-β gene alterations in the later stages of the disease.

Discussion

In this study, we examined the association between TP53 mutations and copy number alterations (CNAs) in TGF-β signaling pathway and their impact on overall survival in breast cancer using data from the TCGA-BRCA cohort. Biological association Fisher's exact test revealed a statistically significant association between TP53 mutation status and TGF-β pathway CNAs (OR = 4.44, 95% CI: 1.61–12.27, p = 0.005). This suggests that TP53-mutated tumors are more likely to harbor concurrent CNAs in TGF-β pathway genes, possibly due to the genomic instability induced by mutant TP53 (50). The strong association between TP53 mutations and TGF-β pathway CNAs (OR = 4.44, p = 0.005) is consistent with the findings of (51), who demonstrated that TP53-mutant tumors exhibit widespread CNAs and that such alterations occur spontaneously in TP53-null mouse models. This suggests that TP53 mutations may create a permissive genomic environment for the acquisition of CNAs in TGF-β pathway genes.

Survival analyses. This biological association, Kaplan–Meier and Cox regression analyses showed no statistically significant difference in overall survival between patients with or without TP53 mutations or between the other analyzed groups. All log-rank p-values were > 0.05. For instance, one study demonstrated that in HR+/HER2- and HER2+ breast cancer subtypes, there was no statistically significant difference in overall survival between TP53-mutant and wild-type cases, with p-values of 0.585 and 0.07, respectively (52). Similarly, other studies have found no significant prognostic impact of TP53 mutations on survival in certain patient subgroups, with Kaplan-Meier curves showing non-significant differences (53). This supports the notion that the prognostic

value of TP53 mutations is complex and may be subtype-dependent, which could explain the lack of a significant effect in our primary analyses. Independent prognostic factors: Multivariable Cox regression confirmed that only older age (HR = 1.04 per year, $p<0.001$) and advanced tumor stage (Stage IV vs. I, HR = 5.78, $p < 0.001$) were independent predictors of inferior overall survival. Neither TP53 mutation nor TGF-β CNA retained prognostic significance after adjustment for clinical covariates.

Interpretation of discrepancies. The apparent discrepancy between TP53's strong association with TGF-β CNAs and the lack of survival impact can be explained by several factors. First, the low number of events (66 deaths out of 479 patients) limited statistical power to detect modest effect sizes. Second, effective adjuvant therapies may mitigate the prognostic impact of these genetic alterations. Third, the association between TP53 and TGF-β CNAs may reflect genomic co-occurrence rather than a functional interaction that directly influences survival. Fourth, the relatively short follow-up time in the TCGA dataset may not capture late recurrences or differences in long-term survival (47).

Compared with previous studies, our results are consistent with numerous TCGA studies indicating that TP53 mutations are related with aggressive tumor patterns, but their effect is not independently consistent on survival after adjusting for disease stage and treatment (45). Changes in the TGF-β pathway remain controversial; no studies have shown any association with survival as reported in reference (23), and it has been shown that the role of TGF-β is contradictory in breast cancer, as it turns from an inhibitor of growth to an inducer of it as the disease progresses, which may explain the conflicting results in the scientific literature [48]. The lack of a significant effect on survival rate in our analysis does not preclude the possibility that specific types of copy number changes such as amplification versus deletion, as well as specific genetic changes such as TGFB1 alone, may have predictive value in selected subgroups.

Conclusions

The attendance of TP53gene mutations is closely related with copy number variation in the TGF-β pathway; however, neither of these variations independently predicts overall survival in breast cancer patients after adjusting for age and disease stage. Future studies should validate these findings in independent cohorts, explore the effects specific to each subtype, and integrate multiple data sets to healthier understand the functional interactions between TP53 and TGF-β signaling.

Declarations

Acknowledgment

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Ethics statement

The author approved that this research follows the journal's Attached Ethic Approval guidelines as appeared on the journal's author guidelines page. This study relies on

publicly available, published data obtained from reliable scientific sources and databases. It did not involve direct sample collection from patients, and therefore, approval from the morals committee was not required. The researchers are committed to using the data for scientific purposes, adhering to the principles of scientific integrity and properly documenting all sources used.

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Competing interest's statement

The authors declare that there are no conflicts of interest, financial or otherwise, that affected on the results or interpretation of this research.

Author contributions

MAF contributed to developing the study concept and design, conducting the practical work, analysing the data, and writing the first draft of the manuscript. BSA participated in data collection and laboratory analysis. The third researcher contributed to the statistical analysis and clarification of the results. Altogether researchers read the last version of the research and approved its publication.

References

1. Gurcan F. Enhancing breast cancer prediction through stacking ensemble and deep learning integration. PeerJ Computer Science. 2025 Feb 3;11: e2461. https://doi.org/10.7717/peerj-cs.2461

2. Munisamy S, Vinayagam MM. ADVANCES IN PHYTOMEDICINE AND THERAPEUTIC APPROACHES FOR EMERGING FRONTIERS IN BREAST CANCER. Biological Sciences Today: Emerging Discoveries and Application. 2025:29.

3. Yersal O, Barutca S. Biological subtypes of breast cancer: Prognostic and therapeutic implications. World journal of clinical oncology. 2014 Aug 10;5(3):412. doi: 10.5306/wjco.v5.i3.412

4. Li Y, Zhang C, Chen J, Tu G, Tang L. FKBP10 expression and TP53 mutation predict prognosis and chemotherapy response in triple-negative breast cancer. Discover Oncology. 2025; 16:1409. https://doi.org/10.1007/s12672-025-03275-8

5. Jing H, Gao Y, Jing L, Yang H, Liu S. Recent advances in therapeutic use of transforming growth factor-beta inhibitors in cancer and fibrosis. Front Oncol. 2025; 15:1489701. https://doi.org/10.3389/fonc.2025.1489701

6. Gottumukkala SB, Ganesan TS, Palanisamy A. Comprehensive molecular interaction map of TGFβ-induced epithelial to mesenchymal transition in breast cancer. NPJ Syst Biol Appl. 2024;10(1):53. DOI: 10.1038/s41540-024-00378-w

7. Hwang SH, Baek SH, Lee MJ, Kook Y, Bae SJ, Ahn SG, et al. Clinical relevance of TP53 mutation and its characteristics in breast cancer with long-term follow-up. Cancers (Basel). 2024;16(23):3899. DOI: 10.3390/cancers16233899

8. Baba AB, Rah B, Bhat GR, Mushtaq I, Parveen S, Hassan R, et al. Transforming growth factor-beta (TGF-β) signaling in cancer: a betrayal within. Front Pharmacol. 2022; 13:791272. DOI: 10.3389/fphar.2022.791272

9. Belizario JE, Loggulo AF. Insights into breast cancer phenotyping through molecular omics approaches and therapy response. Cancer Drug Resist. 2019;2(3):527. doi: 10.20517/cdr.2018.009

10. Waks AG, Winer EP. Breast cancer treatment: a review. JAMA. 2019;321(3):288-300. DOI: 10.1001/jama.2018.19323

11. Smolarz B, Nowak AZ, Romanowicz H. Breast cancer—epidemiology, classification, pathogenesis and treatment: a review. Cancers (Basel). 2022;14(10):2569. DOI: 10.3390/cancers14102569

12. Toi M, Ohashi Y, Seow A, Moriya T, Tse G, Sasano H, et al. Epidemiology, pathology and treatment of breast cancer. Jpn J Clin Oncol. 2010;40(Suppl 1):i13-i18. DOI: 10.1093/jjco/hyq122

13. Kashyap D, Pal D, Sharma R, Garg VK, Goel N, Koundal D, et al. Global increase in breast cancer incidence: risk factors and preventive measures. Biomed Res Int. 2022; 2022:9605439. doi: 10.1155/2022/9605439.

14. Shan R, Dai LJ, Shao ZM, Jiang YZ. Evolving molecular subtyping of breast cancer advances precision treatment. Cancer Biol Med. 2024;21(9):731. doi: 10.20892/j.issn.2095-3941.2024.0222

15. Lopez-Gonzalez L, Sanchez Cendra A, Sanchez Cendra C, Roberts Cervantes D, Cassinello Espinosa J, Pekarek T, et al. Exploring biomarkers in breast cancer: hallmarks of diagnosis, treatment, and follow-up in clinical practice. DOI: 10.3390/medicina60010168

16. Rakha E, Soria D, Green AR, Lemetre C, Powe DG, Nolan CC, et al. Nottingham Prognostic Index Plus (NPI+): a modern clinical decision-making tool in breast cancer. 2014. DOI: 10.1038/bjc.2014.120

17. Gluz O, Hofmann D, Würstlein R, Liedtke C, Nitz U, Harbeck N. Genomic profiling in luminal breast cancer. 2013. DOI: 10.1159/000357535

18. Melhem-Bertrandt A, Bojadzieva J, Ready KJ, Obeid E, Liu DD, Gutierrez-Barrera AM, et al. Early onset HER2-positive breast cancer is associated with germline TP53 mutations. Cancer. 2012;118(4):908-913. DOI: 10.1002/cncr.26377

19. Fu J, Tong Y, Xu Z, Li Y, Zhao Y, Wang T, et al. Impact of TP53 mutations on EGFR-tyrosine kinase inhibitor efficacy and potential treatment strategy. Clin Lung Cancer. 2023;24(1):29-39. DOI: 10.1016/j.cllc.2022.08.007

20. Jasar D, Filipovski V, Kubelka-Sabit K. Clinicopathological and histomorphological association in K-ras mutated colorectal cancer. Virchows Arch. 2022; 481:1-364.

21. Parikh D, Shah M. A comprehensive study on epigenetic signatures to monitor disease progression and response to therapy in breast cancer. Biomed Anal. 2024;1(3):205-217. https://doi.org/10.1016/j.bioana.2024.06.004

22. Zhang Y, Alexander PB, Wang XF. TGF-β family signaling in the control of cell proliferation and survival. Cold Spring Harb Perspect Biol. 2017;9(4):a022145. DOI: 10.1101/cshperspect.a022145

23. Gungor MZ, Uysal M, Senturk S. The bright and dark side of TGF-β signaling in hepatocellular carcinoma: mechanisms, dysregulation, and therapeutic implications. Cancers (Basel). 2022;14(4):940. DOI: 10.3390/cancers14040940

24. Wang X, Zhang L, Si H. Combining luteolin and curcumin synergistically suppresses triple-negative breast cancer by regulating IFN and TGF-β signaling pathways. Biomed Pharmacother. 2024; 178:117221. DOI: 10.1016/j.biopha.2024.117221

25. Syed V. TGF-β signaling in cancer. J Cell Biochem. 2016;117(6):1279-1287. DOI: 10.1002/jcb.25496

26. Sa G, Das T. Anti-cancer effects of curcumin: cycle of life and death. Cell Div. 2008;3(1):14. doi: 10.1186/1747-1028-3-14

27. Hao Y, Baker D, Ten Dijke P. TGF-β-mediated epithelial-mesenchymal transition and cancer metastasis. Int J Mol Sci. 2019;20(11):2767. DOI: 10.3390/ijms20112767

28. Testa U, Castelli G, Pelosi E. Breast cancer: a molecularly heterogeneous disease needing subtype-specific treatments. Med Sci (Basel). 2020;8(1):18. DOI: 10.3390/medsci8010018

29. Gerratana L, Davis AA, Velimirovic M, Clifton K, Hensing WL, Shah AN, et al. Interplay between ESR1/PIK3CA variants and oncogenic pathway alterations in metastatic breast cancer. Breast Cancer Res. 2023;25(1):112. doi: 10.1186/s13058-023-01718-0

30. Sundaramurthy G. A probabilistic approach for automated discovery of biomarkers using expression data from microarray or RNA-Seq datasets [dissertation]. Cincinnati: University of Cincinnati; 2016. doi: 10.1016/j.compbiomed.2015.07.029

31. Lin XY, Guo L, Lin X, Wang Y, Zhang G. Concomitant PIK3CA and TP53 mutations in breast cancer: analysis of clinicopathologic features and prognosis. J Breast Cancer. 2023;26(4):363. doi: 10.4048/jbc.2023.26.e30

32. Ying XH, Zhang KY, Zhu XZ, Jiang SH, Chen L, Li JJ, et al. Integrated genomic profiling identifies predictive biomarkers for neoadjuvant therapy response in breast cancers. 2025. https://doi.org/10.21203/rs.3.rs-7055446/v1

33. Ran R, Ma Y, Wang H, Yang J, Yang J. Treatment strategies for HR+/HER2+ metastatic breast cancer: a review. Front Oncol. 2022; 12:975463. https://doi.org/10.3389/fonc.2022.975463

34. Spugnesi L. Genetic profile of DNA repair genes in triple-negative breast cancer. 2015. https://hdl.handle.net/20.500.14242/130423

35. Zheng Y, Li L, Cai W, Li L, Zhang R, Huang W, et al. Unveiling the role of TGF-β signaling pathway in breast cancer prognosis and immunotherapy. Front Oncol. 2024; 14:1488137. https://doi.org/10.3389/fonc.2024.1488137

36. Menon S. Transcriptomic and metabolic pathway analysis reveals mutated genes p53 and TP53 in cancer. Int J Eng Res Mod Educ. 2021;6(2):10-33. DOI 10.5281/zenodo.5553248

37. Handa S, Chatterjee M, Jan N, Mir MA. The interplay between p53 and the tumor microenvironment in progressing breast cancer. In: p53 in Breast Cancer. CRC Press; 2024. p.263-275. DOI:10.1201/9781003520771-17

38. Ferrari P, Scatena C, Ghilli M, Bargagna I, Lorenzini G, Nicolini A. Molecular mechanisms, biomarkers and emerging therapies for chemotherapy-resistant TNBC. Int J Mol Sci. 2022;23(3):1665. doi: 10.3390/ijms23031665.

39. Chakravarti D, LaBella KA, DePinho RA. Telomeres: history, health, and hallmarks of aging. Cell. 2021;184(2):306-322. DOI: 10.1016/j.cell.2020.12.028

40. Marwah H, Dewangan HK. Synergistic targeting of EGFR, ESR1, BCL2 and TP53 pathways for advanced breast cancer therapy. Curr Cancer Drug Targets. 2025. DOI: 10.2174/0115680096366956250314043513

41. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012;2(5):401-404. doi: 10.1158/2159-8290.CD-12-0095.

42. Dinda S, Sanchez A, Moudgil V. Estrogen-like effects of thyroid hormone on regulation of tumor suppressor proteins p53 and retinoblastoma in breast cancer cells. Oncogene. 2002;21(5):761-768. DOI: 10.1038/sj.onc.1205136

43. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature. 2012;490(7418):61-70. https://doi.org/10.1038/nature11412

44. Donehower LA, Soussi T, Korkut A, Liu Y, Schultz A, Cardenas M, Li X, Babur O, Hsu TK, Lichtarge O, Weinstein JN. Integrated analysis of TP53 gene and pathway alterations in the cancer genome atlas. Cell reports. 2019 Jul 30;28(5):1370-84. DOI: 10.1016/j.celrep.2019.07.001

45. Meric-Bernstam F, et al. Cancer. 2018;124(6):1190-1198

46. Shahbandi A, et al. J Cell Physiol. 2020;235(10):6535-6550

47. Tang, K. H., Tang, Y. J., & Blankenship, R. E. (2011). Carbon metabolic pathways in phototrophic bacteria and their broader evolutionary implications. Frontiers in Microbiology, 2, 165. https://doi.org/10.3389/fmicb.2011.00165

48. Fisher, R. A. (1926). The arrangement of field experiments. Journal of the Ministry of Agriculture of Great Britain, 33, 503-513. DOI: 10.23637/rothamsted.8v61q

49. Kogure, Y., et al. (2023). Landscape of Genetic Alterations Underlying Hallmark Signature Changes in Cancer Reveals TP53 Aneuploidy–driven Metabolic Reprogramming. Cancer Research Communications, 3(2), 281–296. DOI: 10.1158/2767-9764.CRC-22-0073

50. Sandoval RL, Bottosso M, Tianyu L, et al. TP53-associated early breast cancer: new observations from a large cohort. J Natl Cancer Inst. 2024;116(8):1246-1254. doi:10.1093/jnci/djae074

51. Tapper, W., et al. (2008). The influence of genetic variation in 30 selected genes on the clinical characteristics of early onset breast cancer. Breast Cancer Research, 10(6), R105. DOI: 10.1186/bcr2213

52. Akarlar, G. A., et al. (2025). A Multi-Evidence Framework Rescues Low-Power Prognostic Signals and Rejects Statistical Artifacts in Cancer Genomics. arXiv preprint. https://doi.org/10.48550/arXiv.2510.18571

53. Shukla, N., et al. (2022). TGF-β at the crossroads of multiple prognosis in breast cancer, and beyond. Life Sciences, 310, 121011. DOI: 10.1016/j.lfs.2022.121011