

Pan-Cancer Proteomic Profiling Reveals Context-Dependent Dysregulation of TP53 Across Tumor Types and Oncogenic Pathways

Rashmi Gupta

All India Institute of Medical Sciences

Dhiraj Kumar Singh

dheerajkumar.ji@aiims.edu

All India Institute of Medical Sciences

Research Article

Keywords: p53 protein, cell cycle, WNT, HIPPO, NRF2, CPTAC

Posted Date: October 14th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11149736/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Background

The p53 protein, which is a key regulator of genomic stability, cell cycle control, apoptosis, and stress responses, is encoded by TP53, the most commonly mutated tumor suppressor gene in human malignancies. Although TP53 mutations are well-characterized at the genomic level, transcriptomic and mutational data do not always accurately represent protein abundance and functional activity. Therefore, proteomic analysis offers vital information about the functional dysregulation of the p53 pathway in cancer.

Methods

Using uniformly processed Clinical Proteomic Tumor Analysis Consortium (CPTAC) datasets, a pan-cancer analysis of TP53 (p53) protein expression was carried out via the UALCAN online platform. Tumor and matched normal tissues from various cancer types were analyzed for TP53 protein expression. Molecular subtype, patient age, and important oncogenic signaling pathways were used to further stratify breast cancer samples. Protein expression levels were statistically assessed using Student's t-test, displayed using box-and-whisker plots, and analyzed as Z-score-normalized data.

Results

Heterogeneous control of p53 stability and degradation was reflected in significant, cancer-specific variations in TP53 protein expression across tumor types. TP53 expression in breast cancer differed significantly amongst molecular subtypes, with triple-negative breast cancer showing the highest levels. Age-stratified analysis revealed varying p53 expression patterns, suggesting that demographic factors play a role in p53 regulation. A pathway-based stratification emphasized the context-specific modulation of p53 signaling, uncovering distinct TP53 expression patterns associated with alterations in WNT, HIPPO, NRF2, mTOR, RTK, and p53/Rb pathways.

Conclusions

A comprehensive pan-cancer study indicates considerable differences in TP53 protein expression influenced by tumor type, molecular subtype, and the context of signaling pathways. These findings underscore the importance of p53 proteome profiling at both molecular and clinical levels, supporting its application in treatment stratification and the development of biomarkers.

Introduction

The protein p53, often referred to as the "guardian of the genome," is encoded by the TP53 gene, which is one of the most frequently mutated genes found in human cancers (Lane, 1992; Levine, 1997). In response to different physiological stressors, p53 acts as a key transcriptional regulator that oversees vital cellular processes, such as cell cycle arrest, DNA repair, apoptosis, senescence, and metabolic balance to uphold genomic integrity (Vousden & Prives, 2009). These protective mechanisms are compromised when TP53 function is lost or becomes dysregulated, commonly due to mutations. This leads to unregulated proliferation, genomic instability, and resistance to apoptosis (Kandoth et al., 2013). Certain TP53 mutations provide gain-of-function characteristics in addition to loss-of-function effects, which actively encourage tumor growth, metastasis, immune evasion, and treatment resistance (Brosh & Rotter, 2009; Muller & Vousden, 2014).

The functional status of p53 in malignancies may not be adequately reflected by genomic or transcriptome analysis alone since p53 activity and stability are strictly regulated at the post-transcriptional and post-translational levels. Therefore, a more straightforward and biologically significant indicator of p53 pathway dysregulation is provided by proteomic evaluation of TP53 (Zhang et al., 2014). Quantitative assessment of protein abundance, post-translational modifications, and pathway activation states is made possible by mass spectrometry-based proteomics, providing vital information about tumor biology that cannot be obtained at the DNA or RNA level (Mertins et al., 2016). High-quality, consistently processed proteome datasets from various tumor types have been produced by the Clinical proteome Tumor Analysis Consortium (CPTAC), enabling integrative and repeatable pan-cancer analysis (Edwards et al., 2015).

Genomic and transcriptomic studies from large-scale cancer initiatives such as The Cancer Genome Atlas (TCGA) have demonstrated that TP53 is among the most frequently mutated genes across human malignancies, with mutation frequencies exceeding 50% in several tumor types including ovarian, lung, and triple-negative breast cancers (Kandoth et al., 2013; Donehower et al., 2019). However, the functional consequences of these genomic alterations are often manifested at the protein level through altered stability, accumulation, or degradation of the p53 protein. Integrative proteogenomic approaches combining genomic mutation data with quantitative proteomics, such as those enabled by CPTAC datasets, provide a more comprehensive understanding of how TP53 alterations translate into functional dysregulation of oncogenic signaling networks in cancer (Mertins et al., 2016). Therefore, examining TP53 expression within clinically annotated proteomic datasets can help bridge the gap between genomic alterations and their biological and clinical consequences. Standardized access to CPTAC data is made possible by platforms like UALCAN, which facilitate the identification of clinically significant dysregulated proteins and allow for the systematic comparison of protein expression between tumors and matched normal tissues (Chandrashekar et al., 2017). Changes in p53 protein expression have important biological and therapeutic ramifications since p53 overexpression frequently signifies stabilization of mutant protein, whereas decreased levels may suggest increased degradation or loss of function (Soussi & Wiman, 2015). Thus, pan-cancer proteome analysis of TP53 makes it possible to identify tumor-specific dysregulation patterns and lays the groundwork for the development of biomarkers and the categorization of treatments for p53-driven cancers.

Methodology

Data Source and Platform

The UALCAN web portal (<http://ualcan.path.uab.edu>), a popular interactive bioinformatics platform, was used to perform pan-cancer investigation of TP53 (p53) protein expression. The Clinical Proteome Tumor Analysis Consortium (CPTAC) databases, which include high-quality, consistently processed proteome data from a variety of tumor and normal tissue samples, are directly accessible through UALCAN. This platform offers a strong framework for identifying dysregulated proteins with potential biological and clinical implications by enabling researchers to conduct methodical comparisons of protein expression across various cancer types.

Selection of CPTAC Proteomic Data

The CPTAC Analysis module of the UALCAN interface was chosen in order to investigate protein expression levels. A variety of cancer types, including breast, lung, colon, ovarian, endometrial, renal, and others, were included in the search for TP53 gene protein expression data. Corresponding normal tissue samples were used as controls when available. In the present study, TP53 protein expression was analysed across multiple cancer cohorts available in CPTAC with the following sample sizes: breast cancer (normal, n = 18; tumor, n = 125), colon cancer (normal, n = 100; tumor, n = 97), ovarian cancer (normal, n = 25; tumor, n = 100), clear cell renal cell carcinoma (normal, n = 84; tumor, n = 110), uterine corpus endometrial carcinoma (normal, n = 31; tumor, n = 100), lung cancer (normal, n = 111; tumor, n = 111), pancreatic adenocarcinoma (normal, n = 74; tumor, n = 137), head and neck cancer (normal, n = 71; tumor, n = 108), glioblastoma (normal, n = 10; tumor, n = 99), and liver cancer (normal, n = 165; tumor, n = 165). These sample sizes were derived directly from the UALCAN interface and were used in the comparative evaluation of TP53 protein expression across cancer types. This method made it possible to examine TP53 expression patterns in both malignant and non-cancerous settings in great detail.

Protein Expression Quantification

TP53 protein expression levels obtained from UALCAN are reported using Z-scores, which display the relative protein abundance adjusted across all samples within each cancer cohort. Meaningful comparisons between tumor and normal tissues, as well as between other cancer types, are made possible by this standardized normalization approach, which ensures that variations in expression are physiologically interpretable rather than data processing errors.

Visualization of Expression Patterns

To see the distributions of TP53 protein expression for tumor versus normal tissues, UALCAN automatically creates box-and-whisker plots. For every form of cancer, these maps show the median

expression, interquartile range, and total variability. The graphs also provide the sample sizes for each group, which enables evaluation of the data's robustness. These visualizations make cross-cancer comparisons easier and offer a concise and understandable summary of tumor-specific changes in TP53 protein expression.

Statistical Analysis

Statistical comparisons between tumor and normal tissue groups were performed using Student's *t*-test as implemented in the UALCAN platform, and *P*-values were used to determine statistically significant differences in TP53 protein expression across cancer types and defined subgroups. As this study was hypothesis-driven and specifically focused on TP53 protein analysis across predefined groups, correction for multiple hypothesis testing was not applied.

Data Interpretation

The CPTAC datasets used in this research are from clinically defined tumor cohorts that are part of larger proteogenomic cancer studies that integrate genomic, transcriptomic, and proteomic data, even though the main focus of the current study is proteomic evaluation of TP53 expression. As a result, the discovered TP53 protein expression patterns were interpreted in light of previously documented genomic changes and clinically significant tumor features, such as patient demographics and molecular subtype classification. Protein-level variations in connection to known TP53 mutation landscapes described in extensive genomic investigations can be more meaningfully biologically interpreted thanks to this integrative paradigm.

Results

Differential TP53 protein expression across cancers and Breast Cancer subgroups

Pan-cancer analysis of CPTAC proteomic datasets demonstrated significant differences in TP53 (p53) protein expression between tumor and matched normal tissues across multiple cancer types, reflecting cancer-specific dysregulation of p53 at the protein level. Several malignancies exhibited marked upregulation or downregulation of TP53 protein abundance, underscoring the heterogeneous mechanisms governing p53 stability, degradation, and post-translational regulation in different tumor contexts. In breast cancer, stratification by molecular subtype revealed pronounced variability in TP53 protein expression (Fig. 1).

Notably, triple-negative breast cancer showed the highest TP53 protein levels when compared with luminal A, luminal B, and HER2-positive subtypes, consistent with the high prevalence of TP53 alterations in this aggressive subtype. Further age-stratified analysis indicated differential TP53 protein expression across age groups, suggesting that patient age may influence p53 protein regulation,

potentially through age-associated changes in cellular stress responses, genomic instability, or tumor microenvironmental factors.

Together, these observations highlight that TP53 protein expression is not uniform across cancers but is shaped by tumor lineage, molecular subtype, and demographic factors. This heterogeneity emphasizes the complex and context-dependent role of p53 in tumor biology and supports the importance of proteomic-level assessment of TP53 for understanding its functional impact in cancer progression and clinical stratification.

Pathway-specific alterations in TP53 protein expression in breast cancer

Pathway-based stratification of CPTAC breast cancer samples revealed distinct patterns of TP53 protein expression across key oncogenic signaling pathways. Compared with normal breast tissues, tumors harboring alterations in the WNT, HIPPO, p53/Rb, NRF2, mTOR, and RTK pathways demonstrated variable TP53 protein abundance, reflecting pathway-specific modulation of p53 regulation (Fig. 2).

Notably, TP53 expression tended to be reduced in HIPPO- and p53/Rb-altered tumors, whereas increased or heterogeneous expression patterns were observed in tumors associated with NRF2, mTOR, and RTK pathway alterations. WNT pathway–altered tumors also exhibited altered TP53 levels compared to normal samples, indicating potential crosstalk between WNT signaling and p53 regulation. Collectively, these findings suggest that TP53 protein expression in breast cancer is strongly influenced by the underlying molecular pathway alterations, highlighting the context-dependent regulation of p53 within distinct oncogenic signaling networks.

Discussion

In this work, we used CPTAC datasets obtained via the UALCAN platform to perform a thorough pan-cancer proteomic investigation of TP53 (p53) protein expression. Our results emphasize the very context-dependent regulation of p53 in human malignancies by showing significant variation in TP53 protein abundance across various cancer types, breast cancer molecular subtypes, age groups, and pathway-altered tumors. Because genomic and transcriptome changes frequently do not accurately reflect the functional status of the p53 signaling axis, these findings highlight the significance of proteomic-level evaluation (Vousden & Prives, 2009; Donehower et al., 2019).

Tumor and matched normal tissues showed notable variations in TP53 protein expression among malignancies. These proteomic findings are in line with large-scale genomic studies that have documented high TP53 mutation frequencies in a variety of tumor forms, many of which lead to the accumulation and stabilization of mutant p53 proteins (Kandoth et al., 2013; Donehower et al., 2019). While truncating or loss-of-function mutations may be linked to lower protein levels, missense TP53 mutations often result in higher protein abundance due to defective degradation, according to integrative analyses combining genomic mutation patterns with proteomic datasets. Tumor-specific regulatory

mechanisms governing protein stability and the underlying diversity of genomic TP53 changes are therefore probably responsible for the varied TP53 protein expression patterns seen in the current pan-cancer investigation.

This heterogeneity most likely results from variations in the spectrum of TP53 mutations, post-translational modifications, and protein stability mechanisms controlled by molecular chaperone complexes and ubiquitin–proteasome pathways (Brosh & Rotter, 2009). Missense TP53 mutations, which result in transcriptionally deficient but highly stable proteins with gain-of-function characteristics that enhance tumor growth, invasion, and therapy resistance, are often linked to accumulation of p53 protein in tumors (Freed-Pastor & Prives, 2012). On the other hand, loss-of-function mutations, increased degradation, or inhibition by oncogenic signaling networks may be the cause of decreased p53 protein production.

The importance of protein stability mechanisms as tumor suppressor pathway modulators is becoming more widely acknowledged. It has been demonstrated that molecular chaperone complexes, such as R2TP, stabilize carcinogenic proteins and modify cellular proteostasis, thereby indirectly impacting p53-regulated pathways. Our earlier research highlighted how dysregulated proteostasis can contribute to tumor development by demonstrating the role of the R2TP complex in cancer-related protein stabilization, including its involvement in viral oncogenesis and lymphoma biology (Lone et al., 2020; Lone et al., IJRAR).

These results offer a molecular explanation for the varied patterns of p53 protein expression found in the current proteomic research. Subtype-specific investigation of breast cancer showed that triple-negative breast cancer (TNBC) had far higher amounts of TP53 protein than luminal and HER2-positive subtypes.

This finding confirms the accumulation of mutant p53 proteins in aggressive tumor subtypes and is in line with extensive genomic studies that show a high prevalence of TP53 mutations in TNBC (Cancer Genome Atlas Network, 2012; Olivier et al., 2010). Increased mutant p53 has been linked to invasion, metastasis, and the epithelial–mesenchymal transition (EMT). Accordingly, our earlier research emphasized the dual significance of EMT in treatment resistance and cancer development, highlighting its interaction with tumor suppressor failure and signaling plasticity.

Age-related changes in genomic instability, cellular stress responses, and tumor microenvironment composition factors previously connected to cancer susceptibility and progression may have an impact on p53 regulation, according to age-stratified differences in TP53 protein expression seen in breast cancer (Campisi, 2013). These results demonstrate how important it is to include demographic factors in proteomic cancer investigations. Different TP53 protein expression patterns were found across important oncogenic signaling pathways, including as WNT, HIPPO, p53/Rb, NRF2, mTOR, and RTK pathways, according to pathway-based stratification. In cancers changed by HIPPO and p53/Rb, decreased TP53 expression indicates coordinated inactivation of tumor suppressor networks regulating apoptosis and cell cycle arrest (Harvey et al., 2013; Dyson, 2016). On the other hand, tumors changed by NRF2, mTOR, and RTK showed variable or increased TP53 expression, which is probably due to adaptive

metabolic and oxidative stress responses that interact with p53 signaling (Levine, 2020). The intricacy of tumor-specific regulatory networks controlling p53 function is further highlighted by crosstalk between p53 and WNT signalling pathways (Kim et al., 2013). Crucially, the clinical significance of proteostasis-associated pathways in regulating p53-related outcomes is supported by our earlier bioinformatics studies that identified PIH1D1 and p53 as prognostic markers in Pediatric brain tumors and breast cancer (Singh et al., 2025 JABB). The interpretability of p53 dysregulation in various cancer situations is improved by combining such bioinformatics insights with extensive proteome data.

Together, our results show that rather than being consistently regulated across malignancies, TP53 protein expression is influenced by tumor lineage, molecular subtype, signalling pathway changes, and protein stability mechanisms. The translational significance of protein-level research is highlighted by the merging of CPTAC-based proteomic analysis with established literature and our earlier mechanistic and computational studies. In addition to supporting precision oncology tactics meant to restore p53 function or take advantage of weaknesses in p53-deficient tumors, this all-encompassing approach offers a greater knowledge of p53 dysregulation (Bykov et al., 2018).

Conclusion

This study underscores the central role of TP53 dysregulation in cancer and highlights the power of proteomic analysis to capture the functional state of p53 signalling beyond genomic alterations. Pan-cancer evaluation reveals tumor-, subtype-, and pathway-specific differences in p53 protein expression, reflecting context-dependent regulation of stability and activity. The association of p53 alterations with oncogenic pathways and proteostasis regulators, including the R2TP complex, supports a network-driven model of tumor progression. The mechanistic interpretation of TP53 dysregulation is strengthened and the significance of proteogenomic approaches in comprehending cancer biology and enhancing biomarker-driven precision oncology strategies is reinforced when proteomic findings are integrated with previously published genomic mutation landscapes and clinically relevant tumor characteristics. Collectively, these findings emphasize the translational relevance of protein-level TP53 assessment and provide a framework for biomarker discovery and therapeutic targeting in p53-driven malignancies.

Declarations

Author Contribution

Dr. RG and Dr. DKS conceived the idea for the work, designed the overall structure, and performed an extensive literature search and critical analysis of published data and interpreted key findings, prepared all figures and tables, and drafted as well. The final manuscript have been read and approved by both the authors.

Acknowledgement

The authors express their sincere gratitude to their respective institutions for their assistance and facilities. The All India Institute of Medical Sciences Delhi, is acknowledged by Dr. Dhiraj Kumar Singh and Dr. Rashmi Gupta for providing resources and research facilities. Additionally, the authors would like to thank their colleagues and collaborators whose intelligent talks helped to shape this work.

References

1. Vousden, K.H., & Prives, C. (2009). Blinded by the light: The growing complexity of p53. *Cell*, 137(3), 413–431.
2. Brosh, R., & Rotter, V. (2009). When mutants gain new powers: News from the mutant p53 field. *Nature Reviews Cancer*, 9(10), 701–713. <https://doi.org/10.1038/nrc2693>
3. Chandrashekar, D. S., Bashel, B., Balasubramanya, S. A. H., Creighton, C. J., Ponce-Rodriguez, I., Chakravarthi, B., & Varambally, S. (2017). UALCAN: A portal for facilitating tumor subgroup gene expression and survival analyses. *Neoplasia*, 19(8), 649–658. <https://doi.org/10.1016/j.neo.2017.05.002>
4. Edwards, N. J., Oberti, M., Thangudu, R. R., Cai, S., McGarvey, P. B., Jacob, S., Mesri, M. (2015). The CPTAC data portal: A resource for cancer proteomics research. *Journal of Proteome Research*, 14(6), 2707–2713. <https://doi.org/10.1021/pr501254j>
5. Kandoth, C., McLellan, M. D., Vandin, F., Ye, K., Niu, B., Lu, C., ... Ding, L. (2013). Mutational landscape and significance across 12 major cancer types. *Nature*, 502(7471), 333–339. <https://doi.org/10.1038/nature12634>
6. Lane, D. P. (1992). Cancer. p53, guardian of the genome. *Nature*, 358(6381), 15–16. <https://doi.org/10.1038/358015a0>
7. Levine, A. J. (1997). p53, the cellular gatekeeper for growth and division. *Cell*, 88(3), 323–331. [https://doi.org/10.1016/S0092-8674\(00\)81871-1](https://doi.org/10.1016/S0092-8674(00)81871-1)
8. Mertins, P., Mani, D. R., Ruggles, K. V., Gillette, M. A., Clauser, K. R., Wang, P., ... Carr, S. A. (2016). Proteogenomics connects somatic mutations to signalling in breast cancer. *Nature*, 534(7605), 55–62. <https://doi.org/10.1038/nature18003>
9. Muller, P. A. J., & Vousden, K. H. (2014). Mutant p53 in cancer: New functions and therapeutic opportunities. *Cancer Cell*, 25(3), 304–317. <https://doi.org/10.1016/j.ccr.2014.01.021>
10. Soussi, T., & Wiman, K. G. (2015). Shaping genetic alterations in human cancer: The p53 mutation paradigm. *Cancer Cell*, 28(4), 404–406. <https://doi.org/10.1016/j.ccell.2015.09.001>
11. Zhang, B., Wang, J., Wang, X., Zhu, J., Liu, Q., Shi, Z., Zhang, Z. (2014). Proteogenomic characterization of human colon and rectal cancer. *Nature*, 513(7518), 382–387. <https://doi.org/10.1038/nature13438>

12. Olivier, M., Hollstein, M., & Hainaut, P. (2010). TP53 mutations in human cancers: Origins, consequences, and clinical use. *Cold Spring Harbor Perspectives in Biology*, 2(1), a001008.
13. Cancer Genome Atlas Network. (2012). Comprehensive molecular portraits of human breast tumours. *Nature*, 490(7418), 61–70.
14. Freed-Pastor, W. A., & Prives, C. (2012). Mutant p53: One name, many proteins. *Genes & Development*, 26(12), 1268–1286.
15. Harvey, K. F., Zhang, X., & Thomas, D. M. (2013). The Hippo pathway and human cancer. *Nature Reviews Cancer*, 13(4), 246–257.
16. Dyson, N. J. (2016). RB1: A prototype tumor suppressor and an enigma. *Genes & Development*, 30(13), 1492–1502.
17. Campisi, J. (2013). Aging, cellular senescence, and cancer. *Annual Review of Physiology*, 75, 685–705.
18. Kim, N. H., Kim, H. S., Li, X. Y., et al. (2013). A p53/miR-34 axis regulates Snail1-dependent cancer cell epithelial–mesenchymal transition. *Journal of Cell Biology*, 201(3), 417–433.
19. Donehower, L. A., Soussi, T., Korkut, A., et al. (2019). Integrated analysis of TP53 gene and pathway alterations in The Cancer Genome Atlas. *Cell Reports*, 28(5), 1370–1384.e5.
20. Levine, A. J. (2020). p53 and the immune response: 40 years of exploration. *Cell Death & Differentiation*, 27(1), 1–15.
21. Bykov, V. J. N., Eriksson, S. E., Bianchi, J., & Wiman, K. G. (2018). Targeting mutant p53 for efficient cancer therapy. *Nature Reviews Cancer*, 18(2), 89–102.
22. Singh, D. K., Jit, B., Gupta, R., Verma, A. K., & Mir, R. A. (2025). Bioinformatics analysis reveals PIH1D1 as an important prognostic marker in breast cancer. *Journal of Applied Biology & Biotechnology*, 13(1), 202–212. <https://doi.org/10.7324/JABB.2024.189230>
23. Lone, M., Akhter, Q., Kumar, M., et al. (2020). Role of R2TP complex in lymphoma and its therapeutic potential. *International Journal of Advanced Research*, 8(11), 300–303.
24. Lone, M., Kumar, M., & Kumar, D. (Year). Functional enrichment analysis and network interaction of R2TP complex. *International Journal of Research and Analytical Reviews*.

Figures

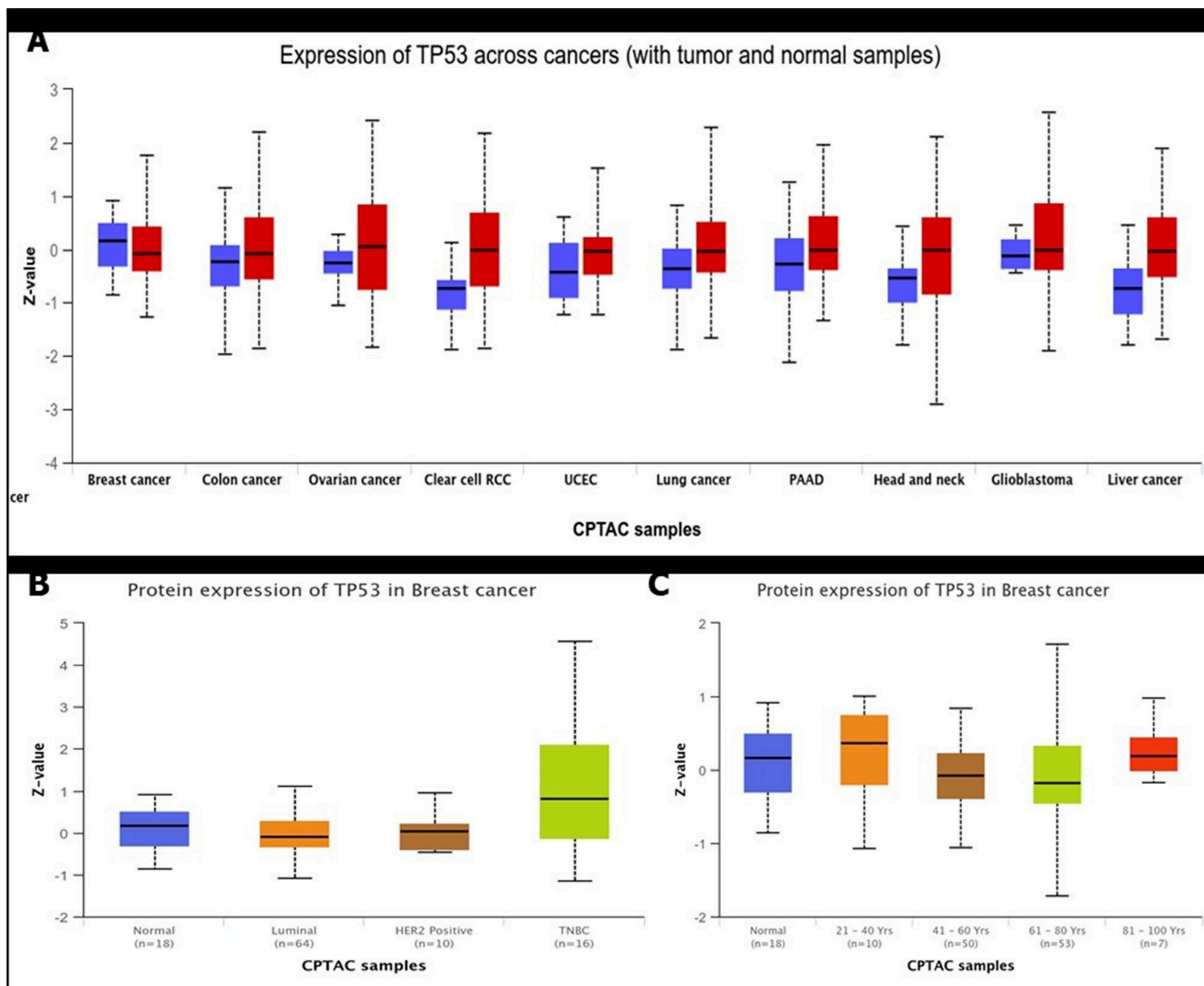


Figure 1

TP53 (p53) protein expression across cancers and breast cancer subgroups. (A) Pan-cancer analysis of TP53 protein expression comparing tumor and normal tissues across multiple cancer types using CPTAC datasets. **(B)** TP53 protein expression across breast cancer molecular subtypes, with luminal, HER2-positive, and TNBC. **(C)** TP53 protein expression in breast cancer stratified by patient age groups. Data are presented as box plots showing Z-score-normalized protein expression; center lines indicate medians, boxes represent interquartile ranges, and whiskers denote data range.

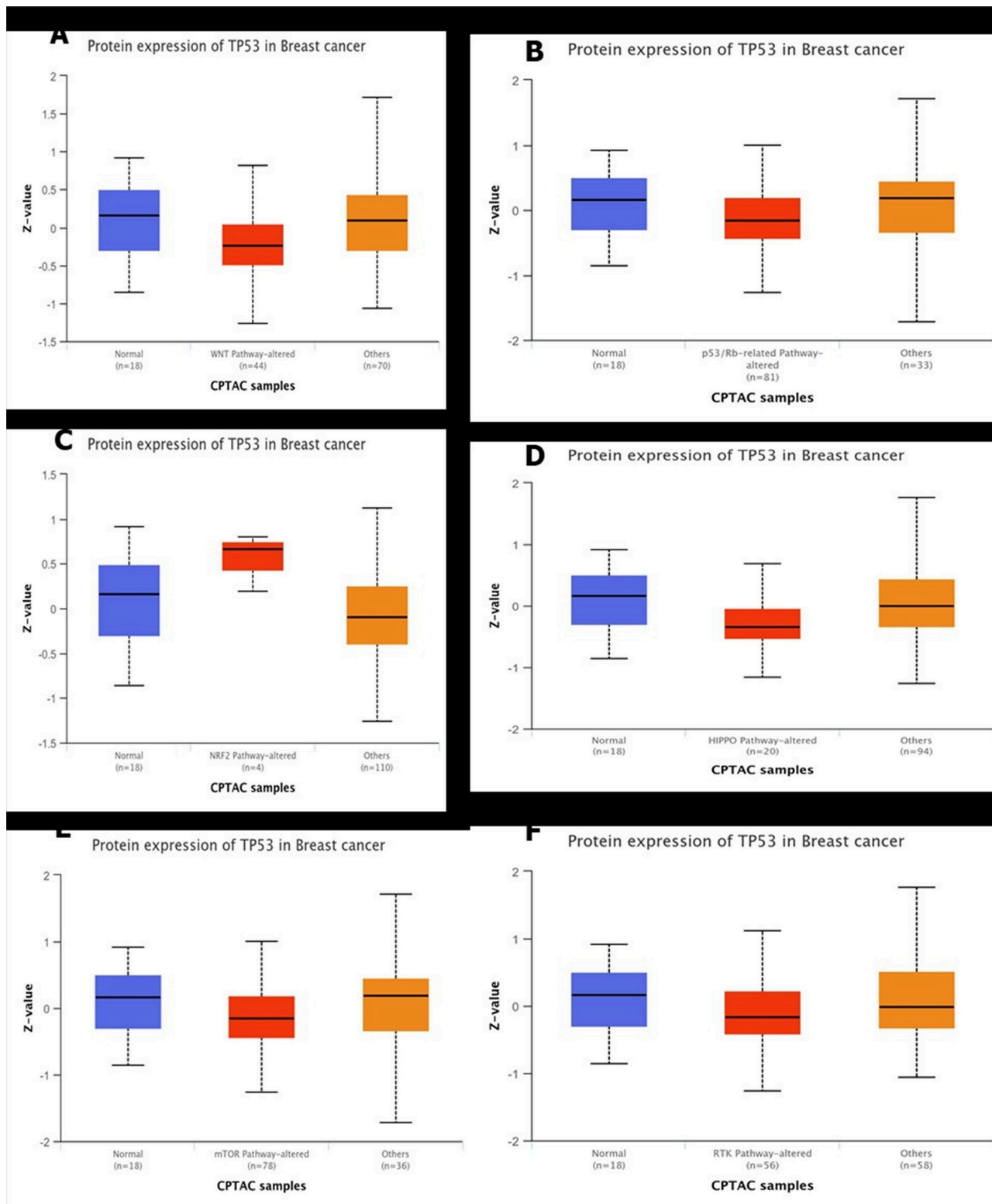


Figure 2

Pathway-specific TP53 protein expression in breast cancer. Box plots show TP53 protein expression (Z-scores) in CPTAC breast cancer samples stratified by alterations in major signaling pathways: **(A)** WNT, **(B)** p53/Rb-related, **(C)** NRF2, **(D)** HIPPO, **(E)** mTOR, and **(F)** RTK. Pathway-altered tumors are compared with normal breast tissues and unclassified tumors ("Others"). Boxes indicate interquartile range, center

lines denote medians, and whiskers represent data dispersion. Distinct expression patterns suggest pathway-dependent regulation of TP53 in breast cancer.