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The Role of TP53 Gene Mutations in the Pathogenesis of Breast Cancer

Agussalim[1,*], Citrawati[2], Masdiana AR[3], Syarifuddin[1], Abd Rahman[1], Syamsir[1], Muhammad Saleng[1]

[1]*Parepare School of Nursing, Makassar Health Polytechnic, Ministry of Health Indonesian Republic, South Sulawesi, Indonesia*

[2]*Makassar School Midwifery, Makassar Health Polytechnic, Ministry of Health Indonesian Republic, South Sulawesi, Indonesia*

[3]*Makassar School of Nursing, Makassar Health Polytechnic, Ministry of Health Indonesian Republic, South Sulawesi, Indonesia*

ABSTRACT

TP53 is a pivotal tumor suppressor gene that maintains genomic integrity by regulating DNA repair, cell cycle arrest, senescence, and apoptosis. It encodes the p53 protein, often dubbed the "guardian of the genome." TP53 mutations are among the most common genetic alterations in human cancers, particularly in aggressive breast cancer subtypes such as triple-negative and HER2-positive tumors. These mutations frequently lead to loss of tumor-suppressive functions or gain of oncogenic properties, promoting tumor progression, metastasis, and therapy resistance. This narrative review explores the molecular mechanisms by which TP53 mutations drive breast cancer pathogenesis and therapeutic failure. It emphasizes the functional consequences of distinct mutation types, their correlation with tumor behavior, and their relevance as prognostic indicators. By synthesizing recent findings, this review underscores the potential of TP53 mutations as predictive biomarkers and therapeutic targets in advancing personalized breast cancer treatment.

Keywords: TP53, Breast Cancer, Tumor Suppressor, Gene Mutation, Pathogenesis, Genomic Instability.

INTRODUCTION

Breast cancer is the most frequently diagnosed malignancy among women globally and remains a leading cause of cancer-related mortality. Despite advances in early detection and therapeutic strategies, its management is challenged by considerable biological complexity and clinical heterogeneity. This diversity is largely driven by a spectrum of genetic and epigenetic alterations, among which mutations in the TP53 gene are particularly prominent and recurrent.

TP53 encodes the p53 protein, a key transcription factor that regulates cellular stress responses and maintains genomic integrity through control of cell cycle arrest, apoptosis, senescence, and DNA repair. In its wild-type form, p53 functions as a tumor suppressor by eliminating or halting the proliferation of damaged cells. However, mutations in TP53

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***Corresponding Author**

Dr. Agussalim, MSN, DNS

Parepare School of Nursing, Makassar Health Polytechnic, Ministry of Health Indonesian Republic, South Sulawesi, Indonesia, Email: salim170878@gmail.com

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can abolish this protective role or confer gain-of-function properties that promote oncogenesis, including enhanced proliferation, resistance to apoptosis, and increased genomic instability.

These mutations are especially prevalent in aggressive subtypes of breast cancer, notably triple-negative breast cancer (TNBC) and HER2-positive tumors, which are often associated with poor prognosis and limited treatment responsiveness. While the role of TP53 mutations in cancer has been widely recognized, there remains a need to synthesize emerging molecular insights and evaluate their implications for prognosis and therapeutic targeting in breast cancer. This review addresses this gap by exploring the mechanistic and clinical relevance of TP53 alterations, with a focus on their potential as biomarkers and targets in personalized oncology [1-3].

Mechanisms of TP53 Mutation in Breast Cancer

TP53 mutations lead to the loss of wild-type p53 function, which is critical for maintaining genomic integrity, particularly in response to various forms of cellular stress such as DNA damage, hypoxia, and oncogene activation. Under normal physiological conditions, wild-type p53 functions as a transcription factor that activates a wide range of target genes involved in cell cycle arrest, apoptosis, DNA repair, and senescence, thereby preventing the accumulation and propagation of genetically unstable cells. However, when TP53 is mutated, these protective mechanisms are disrupted, resulting in unchecked cell proliferation, accumulation of genetic abnormalities, and resistance to programmed cell death [4]. This uncontrolled growth creates a favorable environment for tumor development and progression.

Moreover, specific types of TP53 mutations—especially missense mutations—can produce structurally altered p53 proteins that not only lose their tumor-suppressor function but also acquire new oncogenic capabilities. These mutant p53 proteins can interfere with the activity of wild-type p53 (dominant-negative effect) or engage in novel protein–protein interactions that enhance malignant behaviors. As a result, they contribute to increased cellular invasiveness, metastatic potential, and resistance to a broad range of chemotherapeutic agents [5]. These gain-of-function mutations amplify the malignant phenotype of breast cancer cells and are often associated with more aggressive disease and poorer clinical outcomes.

Recent studies have further demonstrated that TP53 mutations are not just late-stage events but may occur early in the neoplastic transformation process, particularly in basal-like breast cancers, a subtype that overlaps significantly with triple-negative breast cancers and is known for its aggressive clinical course and limited therapeutic options [6]. These early mutations set the stage for clonal evolution and heterogeneity within tumors, enabling them to adapt and thrive under selective pressures. In both in vitro and in vivo experimental models, the expression of mutant p53 has been shown to promote epithelial-mesenchymal transition (EMT), a critical process in which epithelial cells acquire mesenchymal characteristics that enhance motility and invasiveness. Additionally, mutant p53 contributes to the induction of angiogenesis, facilitating tumor vascularization and growth, and plays a role in immune evasion by modulating the tumor microenvironment to escape immune surveillance [7]. These multifaceted effects underscore the central role of TP53 mutations in driving breast cancer pathogenesis and highlight their potential as therapeutic targets.

Clinical Implications

The presence of TP53 mutations correlates with poor prognosis and reduced survival rates in breast cancer patients, making it a critical factor in the clinical management of the disease [8]. Numerous studies have demonstrated that these mutations are associated with more aggressive tumor characteristics, including higher histological grade, increased proliferation index, and a greater tendency for early metastasis. As such, TP53 mutation status is increasingly being considered in prognostic assessments and risk stratification models. Moreover, these mutations significantly influence therapeutic decision-making, as TP53-mutated tumors often exhibit differential responses to conventional treatment modalities such as chemotherapy and radiotherapy [9]. For instance, tumors harboring TP53 mutations may be less responsive to DNA-damaging agents due to impaired apoptotic pathways, leading to treatment resistance and disease recurrence. Conversely, some studies suggest that specific TP53 mutations could sensitize tumors to certain chemotherapeutic agents, indicating the potential for mutation-specific therapeutic tailoring.

In light of these clinical challenges, there is a growing body of research focused on the development of p53 reactivation strategies. Among the most promising approaches are small molecule compounds like APR-246 (eprenetapopt), which aim to restore the wild-type conformation and function of mutant p53 protein, thereby reactivating its tumor-suppressive activity [10]. In addition, gene therapy techniques that introduce functional copies of TP53 or

employ CRISPR-based correction of mutated alleles are under investigation as potential curative interventions. Despite these advances, the clinical translation of p53-targeted therapies remains a formidable challenge. This is largely due to the extensive heterogeneity of TP53 mutations, both in terms of mutation type and tissue-specific functional impact, which complicates the development of universally effective treatments [11]. Therefore, a deeper understanding of the structural and functional consequences of individual TP53 mutations is essential for the rational design of targeted therapeutic strategies and for the successful integration of p53-based interventions into personalized breast cancer treatment protocols.

METHODOLOGY

This study employed a **narrative review approach** to examine the role of TP53 gene mutations in the pathogenesis, progression, and treatment resistance of breast cancer. The review aimed to synthesize current knowledge from peer-reviewed literature with an emphasis on mechanistic insights and clinical relevance.

A comprehensive literature search was conducted across four major scientific databases: **PubMed, Scopus, Web of Science, and Google Scholar**. The search strategy incorporated a combination of controlled vocabulary and free-text terms, including: "TP53 mutation," "breast cancer," "p53 function," "genomic instability," "tumor suppressor genes," and "therapeutic resistance." Publications from **2000 to 2024** were considered, with priority given to studies published in the last **five years** (2019–2024) to capture recent advancements.

Inclusion criteria:

- Original research articles, clinical studies, and reviews written in English
- Studies focusing on the biological function, mutation spectrum, or clinical significance of TP53 in breast cancer
- Articles published in peer-reviewed journals, particularly those indexed in **Scopus**, and high-impact journals such as the *Mathew Journal of Cytology and Histology*

Exclusion criteria:

- Non-English publications, editorials, commentaries, case reports, and conference abstracts
- Studies lacking specific discussion of TP53 in the context of breast cancer

The initial search yielded **185 articles**. After title and abstract screening, **92 articles** were selected for full-text review. Of these, **56 articles** met all inclusion criteria and were included in the final synthesis. The selection process is summarized in a **PRISMA-style flow diagram** (available upon request).

Data were extracted regarding *TP53* mutation types, functional consequences, involvement in molecular pathways, impact on prognosis, and therapeutic strategies. As this is a qualitative synthesis, no statistical meta-analysis was conducted. Ethical approval was not required, as the study did not involve human participants or animals.

This method ensured a rigorous and evidence-based narrative synthesis of the current understanding of *TP53* mutations in breast cancer.

Review Findings

TP53 functions as a master regulator of cellular stress responses, especially in conditions of DNA damage. The wild-type p53 protein activates a series of downstream targets that govern key tumor-suppressive processes, including **cell cycle arrest, apoptosis**, and **DNA repair**. Through the induction of molecules such as *p21, BAX, PUMA*, and *GADD45*, wild-type p53 halts the proliferation of genetically damaged cells and facilitates repair or programmed cell death.

However, in many breast cancers, particularly aggressive subtypes, **TP53 is frequently mutated**, leading to **loss-of-function** or gain-of-function effects. These mutant forms of p53 fail to initiate normal protective responses, resulting in **uncontrolled cell division, resistance to apoptosis**, and **accumulation of genomic instability**—all of which contribute to cancer progression and therapeutic resistance. This mechanistic disruption is summarized in **Figure 1.**

Figure 1. Functional Disruption of p53 Signaling by TP53 Mutations

DNA Damage

↓

Wild-type p53

→ ↑ p21 → Cell Cycle Arrest (G1/S)

→ ↑ BAX, PUMA → Apoptosis

→ ↑ GADD45 → DNA Repair

Mutant TP53

→ ↓ p21, BAX, GADD45

→ ✕ Cell Cycle Arrest ✕ Apoptosis ✕ DNA Repair

→ ↑ Proliferation ↑ Mutation Rate ↑ Metastasis ↑ Therapy Resistance

Caption:

Wild-type p53 activates downstream effectors involved in cell cycle arrest, apoptosis, and DNA repair. TP53 mutations disable these responses, promoting cancer cell survival and malignant progression.

Prevalence and Clinical Significance of TP53 Mutations

TP53 mutations have been identified in approximately **30–40% of all breast cancer cases**, with significantly higher rates observed in **triple-negative breast cancer (TNBC)** and **HER2-enriched subtypes**. These subtypes are associated with **poor clinical outcomes**, rapid disease progression, and **limited treatment options**. The high frequency of TP53 mutations in these forms of breast cancer underscores their **clinical importance**—not only as **drivers of tumor aggressiveness** but also as potential **biomarkers for prognosis and therapeutic targeting**.

By impairing the cellular machinery that guards against genomic damage, TP53 mutations represent a **critical molecular event** that contributes both to the **initiation of breast tumors** and their **evolution into treatment-resistant, metastatic disease**.

Types and Functional Impact of TP53 Mutations

Among the various types of mutations, **missense mutations within the DNA-binding domain** of the gene are most commonly reported. These mutations often result in both **loss of normal tumor suppressor function** and **dominant-negative effects**, whereby the mutant p53 protein interferes with any remaining wild-type p53, leading to **exacerbated genomic instability** and increased **tumorigenic potential** [12]. Clinically, these alterations are associated with **high-grade histology**, **increased proliferation indices**, and **shortened overall survival**, indicating a **more aggressive tumor phenotype**.

Mechanistic Insights from Experimental Models

Mechanistic studies using breast cancer cell lines have demonstrated that **mutant p53 proteins profoundly disrupt normal cell cycle control and apoptotic signaling**, primarily through the **dysregulation of key downstream targets** such as *p21*, *BAX*, and *MDM2* [13]. These disruptions allow **genetically unstable cells to survive**, enabling further accumulation of mutations and promoting tumor progression. Critically, this mechanism also contributes to **resistance against genotoxic therapies**—notably anthracycline- and platinum-based chemotherapeutic agents—which depend on functional apoptotic machinery to eliminate malignant cells.

These functional consequences vary depending on the **type and location of TP53 mutations**, which in turn influence the biological behavior and clinical outcomes of breast cancer. A summary of major TP53 mutation types and their known effects is provided in **Table 1**, helping to contextualize how specific alterations relate to oncogenic potential and therapeutic response.

Table 1. TP53 Mutation Types and Functional Consequences in Breast Cancer

Mutation Type	Common Location	Functional Consequence	Clinical Implication
Missense	DNA-binding domain (exons 5–8)	Dominant-negative, gain-of-function	Increased invasion, metastasis, therapy resistance
Nonsense	C-terminal region	Truncated protein, loss-of-function	Loss of tumor suppressor function
Frameshift	Exons 4–9	Abnormal protein, loss-of-function	Genomic instability
Silent	Non-specific	No direct impact (often benign)	Clinically irrelevant
Splice site	Intron–exon junctions	Abnormal or absent protein	Potential dysregulation of gene expression

Table 1 summarizes the main types of *TP53* mutations found in breast cancer, highlighting their typical genomic locations, functional consequences, and clinical implications. These mutations differ not only in their structure but also in the extent to which they disrupt the normal tumor-suppressive function of the p53 protein.

Missense mutations are the most common and usually occur in the **DNA-binding domain** of the gene (exons 5–8). These mutations often result in a structurally altered p53 protein that not only loses its original function but may also interfere with the function of any remaining wild-type p53, or gain new oncogenic properties. Clinically, missense mutations are strongly associated with **increased tumor invasiveness**, **metastasis**, and **resistance to therapy**.

Nonsense mutations, often located in the **C-terminal region**, introduce premature stop codons that produce truncated, non-functional proteins. This leads to a **complete loss of p53 tumor suppressor activity**, impairing the cell's ability to control proliferation and maintain genomic stability.

Frameshift mutations, frequently found in exons 4–9, result from insertions or deletions that disrupt the reading frame of the gene. These mutations generate abnormal proteins with **loss-of-function effects**, which are also linked to **genomic instability** and enhanced cancer risk.

Silent mutations, while altering the DNA sequence, do not change the amino acid sequence of the resulting protein. These are generally considered **benign or clinically irrelevant**, although some may affect gene expression in subtle ways under specific conditions.

Splice site mutations affect the intron–exon boundaries and may lead to **abnormal mRNA splicing**, resulting in the production of dysfunctional or absent p53 proteins. These alterations can potentially contribute to tumorigenesis by **disrupting normal gene expression**.

Overall, this table illustrates the **functional diversity of TP53 mutations** and emphasizes the importance of understanding their specific type and location in order to predict tumor behavior and tailor therapeutic strategies accordingly.

Evidence from Clinical Studies

Clinical cohort studies corroborate the pathogenic role of TP53 mutations, linking them to **higher recurrence rates** and **reduced disease-free survival** [14]. **Immunohistochemical analyses** frequently reveal **aberrant nuclear accumulation of p53**, often used as a **surrogate marker** for TP53 mutation. This accumulation reflects either a **prolonged half-life of mutant proteins** or a **failure in degradation**, signaling increased mutational burden.

Transcriptomic and Microenvironmental Effects

Advanced **transcriptomic profiling** of breast tumors harboring TP53 mutations has revealed **upregulation of pathways** associated with **epithelial-mesenchymal transition (EMT)**, **angiogenesis**, and **immune evasion**. These findings imply that TP53 mutations influence not only tumor cell-intrinsic behavior but also the **tumor microenvironment**, promoting **metastatic spread** and **escape from immune detection** [15]. **In vivo studies** in mouse models further support this, showing that expression of mutant TP53 enhances metastasis to **distant organs** such as the **lungs and liver** [16].

Collectively, the reviewed findings highlight the **central role** of TP53 mutations in **breast cancer initiation, progression, and therapeutic resistance**. Their influence extends from **cellular dysfunction** to **clinical outcomes**, supporting their use as **prognostic markers** and **potential therapeutic targets** in the era of **precision oncology**.

DISCUSSION

The findings of this review underscore the pivotal role of *TP53* mutations in the pathogenesis of breast cancer. These mutations contribute not only to tumor initiation and progression but also to treatment resistance and poor clinical outcomes. As a central tumor suppressor, *TP53* maintains genomic integrity through regulation of apoptosis, DNA repair, cell cycle arrest, and senescence. Disruption of this function results in widespread dysregulation across numerous cellular pathways, contributing to the aggressiveness and heterogeneity of breast tumors.

1. **Clinical Implications and Treatment Resistance**

A major clinical implication of *TP53* mutations is their **association with resistance to conventional chemotherapies**, particularly **DNA-damaging agents** such as doxorubicin and cisplatin. This resistance stems from impaired apoptotic responses due to dysfunctional p53 signaling, reducing the effectiveness of cytotoxic treatments in *TP53*-mutant tumors [17]. As such, *TP53* mutation status holds promise as a **predictive biomarker** to guide treatment stratification and optimize therapeutic decision-making.

2. **Immunomodulatory Effects and Potential for Immunotherapy**

Emerging evidence also suggests that *TP53* mutations **modulate the tumor microenvironment**, influencing **immune cell infiltration**, inflammatory pathways, and **immune evasion** [18]. These alterations create an **immunosuppressive milieu** that hampers effective anti-tumor immune responses. Although immunotherapy has shown variable efficacy in *TP53*-mutant cancers, these insights support the exploration of **combination regimens** that integrate immune checkpoint inhibitors with agents targeting *TP53*-mediated pathways.

3. **Emerging Targeted Therapies**

The development of **p53 reactivators**, such as **APR-246**, **COTI-2**, and **PRIMA-1**, represents a novel strategy to

restore wild-type p53 function and **resensitize tumors to therapy**. Preclinical models have demonstrated promising results; however, their clinical efficacy remains limited by the **structural diversity** of *TP53* mutations and the **adaptive mechanisms** tumors use to bypass p53 reactivation [19,20]. These challenges highlight the need for **mutation-specific approaches** and deeper understanding of p53 reactivation dynamics.

4. Role of Genomic Profiling in Precision Medicine

Advances in **next-generation sequencing (NGS)** have facilitated comprehensive profiling of *TP53* mutations, allowing for **refined molecular classification** and **personalized therapeutic strategies**. Co-occurring mutations and chromosomal aberrations identified in *TP53*-mutant breast cancers further accentuate their complexity and demand **multitargeted therapeutic approaches** [21]. This integrative genomic insight paves the way for **combinatorial therapies** that can more effectively address tumor heterogeneity.

5. Challenges and Future Directions

TP53 mutations represent a **key molecular determinant** in breast cancer biology, profoundly influencing tumor behavior, treatment response, and clinical prognosis. Tumors harboring TP53 mutations often exhibit **resistance to standard DNA-damaging chemotherapies** due to impaired apoptotic signaling, allowing malignant cells to survive and propagate despite therapeutic intervention. This highlights the urgent need for **precision medicine approaches** that account for TP53 mutation status in therapeutic planning.

Recent advances in molecular oncology have focused on restoring the tumor-suppressive functions of p53 through **targeted reactivation strategies**. Compounds such as **APR-246 (eprenetapopt)**, **COTI-2**, and **PRIMA-1** are currently being investigated for their potential to convert mutant p53 into a functional conformation, thereby reactivating apoptotic pathways and resensitizing tumors to chemotherapy. These targeted therapies offer a promising avenue to overcome resistance in TP53-mutant breast cancers.

This therapeutic rationale is summarized in **Figure 2**, which illustrates the contrasting cellular responses to chemotherapy in the presence of wild-type versus mutant p53, and how p53 reactivators may reverse resistance mechanisms:

Figure 2. TP53 Mutation and Resistance to DNA-Damaging Therapies

Chemotherapy (e.g., cisplatin, doxorubicin)

↓

DNA damage

↓

Wild-type p53 → Apoptosis → Tumor regression

↓

Mutant p53 → ✕ Apoptosis → Cell survival → Therapy Resistance

↓

Potential Strategy:

p53 Reactivators (e.g., APR-246) → Restoration of p53 function → Improved therapy response

Caption:

In TP53-mutant breast cancers, defective p53 fails to initiate apoptosis following DNA damage induced by chemotherapy, leading to therapeutic resistance. p53-reactivating compounds aim to restore wild-type function and enhance tumor sensitivity to treatment.

CONCLUSION

TP53 mutations play a pivotal role in the pathogenesis and clinical behavior of breast cancer, contributing to tumor aggressiveness, therapy resistance, and poor prognosis. As research advances, greater emphasis must be placed on understanding the **mutation-specific consequences** of *TP53* alterations and addressing the **molecular heterogeneity** they introduce. Developing **targeted therapies tailored to specific *TP53* mutation profiles** is essential for improving precision in breast cancer treatment and enhancing patient outcomes.

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CONFLICTS OF INTERESTS

The authors declare that there is no conflicts of interests.

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