TP53 mutations and SNPs as prognostic and predictive factors in patients with breast cancer (Review)

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Abstract. Tumor protein 53 (*TP53*) is a tumor suppressor gene that encodes tumor protein p53. Tumor protein p53 regulates the expression of target genes in response to cellular stress. Additionally, p53 participates in the regulation of cell cycle checkpoints, DNA repair and apoptosis. Mutations in the *TP53* gene are associated with numerous types of human cancer, including breast cancer, sarcomas, brain tumors and adrenal cortical carcinomas. In breast cancer, *TP53* mutations are a negative prognostic factor. Tumors with *TP53* mutations are more likely to be aggressive (triple-negative or human epidermal growth factor receptor 2-positive breast cancer), and resistant to chemotherapy and radiotherapy. In addition to a well-known *TP53* mutation, a number of single nucleotide polymorphisms have been systematically identified and evaluated in human populations. In the present article, the role of *TP53* mutations and polymorphisms in clinical practice and breast cancer treatment has been described. Additionally, the existing data on *TP53* polymorphisms in breast cancer as prognostic and predictive factors have been summarized. A literature search of these topics was performed through PubMed and abstracts of the main cancer congresses in recent years.

Contents

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1. Introduction

Tumor protein (*TP53*) is a tumor suppressor gene that encodes tumor protein p53. The p53 protein is situated in the cell nuclei and binds directly to DNA. p53 participates in the regulation of cell cycle checkpoints, DNA repair and apoptosis, and regulates the repair process in response to damaging factors, including chemicals, radiation and ultraviolet rays from sunlight. If the DNA is mutated or damaged and cannot be repaired, p53 transmits a signal, which triggers cell apoptosis and prevents cells from dividing and developing into tumors (1).

Inherited *TP53* gene mutations (germline mutations) increase the risk of numerous cancer types, including breast cancer, leukemia, sarcomas, central nervous system (CNS) tumors and adrenal cortical cancer [as part of Li-Fraumeni syndrome (LFS)] (2). Certain studies have demonstrated that breast cancer in females with LFS has a positive hormone receptor status and human epidermal growth factor receptor (HER)-2/neu overexpression (3,4). In a previous study, TP53 mutations were observed in 2-3% of patients with early-onset breast cancer (5). Somatic mutations in *TP53* occur in ~40% of all cases of breast cancer and occur more frequently than inherited mutations (6). In breast cancer, *TP53* mutations are a negative prognostic factor (7). Tumors with *TP53* mutations are more likely to be aggressive (triple-negative or HER-2-positive breast cancer) (8,9). *TP53* mutations occur at an increased frequency in triple-negative breast cancer in comparison with non-triple-negative cancers (10,11). Furthermore, *TP53* mutations have been indicated to be associated with chemoresistance (10,12,13).

Additionally, *TP53* is also a polymorphic gene. Single nucleotide polymorphisms (SNPs) occur when a single nucleotide is replaced with another, and it is the most common type of change in DNA (14). These changes may affect the function of the p53 protein, and consequently affect cancer risk, progression or response to treatment. Currently, 80 SNPs have been identified in human populations; the majority of SNPs (90%) are situated in introns, outside splice sites or in noncoding exons. However, the potential role of SNPs in breast cancer risk remains to be elucidated (15).

The present study aimed to establish the role of *TP53* mutations and polymorphisms in clinical practice and in breast cancer treatment.

2. Mechanism of action

TP53 is located on chromosome 17 (17p13.1) and encodes p53, which is a phosphoprotein that is composed of 393 amino acids. p53 consists of four domains: i) a N-terminal sequence (transactivation) domain that is involved in the regulation of the target gene transcription; ii) a core domain that recognizes specific DNA sequences; iii) an oligomerization domain that is responsible for the tetramerization of the protein (the functional form of p53); iv) and a C-terminal domain that is essential for the regulation of p53 activity. The C-terminal domain is modified by kinases, acetylases and glycosylases, and binds with other proteins (16). The transactivation domain is also responsible for interactions with the mouse double minute 2 homolog (MDM2) protein, which has ubiquitin ligase activity and is responsible for controlling the proteasomal degradation of p53 (16).

The p53 protein binds DNA and affects the formation of p21, which interacts with a cell division-stimulating protein (cyclin-dependent kinase 2; CDK-2). When p21 binds with CDK-2, this 2 blocks transition to the next stage of the cell cycle (17). Mutations in *TP53* encode proteins that do not have the ability to bind DNA effectively, resulting in uncontrollable cell division and ultimately tumor formation (18).

In healthy cells, the level of p53 protein remains stable and is regulated by the modulation of p53 degradation. In response to DNA damage and other stress signals, p53 protein expression may increase and affect a number of biological mechanisms, including growth arrest, DNA repair and apoptosis. Under such circumstances, the cell cycle stops, and this prevents the replication of damaged DNA. Furthermore, during growth arrest, p53 activates the transcription of proteins that are involved in DNA repair (19). However, the failure of repair mechanisms, as a result of a defective p53, may result in the proliferation of abnormal cells and the promotion of cancer (18).

The cellular level of p53 is tightly regulated via the control of protein accumulation and cellular localization (19). The regulation process is performed via covalent modification of the p53 protein or by interaction with different factors, which causes p53 activation or deactivation in response to stress. A major regulator of p53 is the *MDM2* gene, which encodes a specific ubiquitin ligase: MDM2. MDM2 causes the degradation of p53 via the ubiquitin system in proteasomes (20). MDM2 is encoded by a *TP53*-responsive gene (with *TP53* being a transcriptional activator). Phosphorylation of p53 at Ser15, Thr18 or Ser20 disrupts its binding with MDM2 (21). In normal cells, phosphorylation does not occur, and p53 remains at a low level, which is regulated by MDM2. DNA damage activates protein kinases, including ATM serine/threonine kinase, DNA-dependent protein kinase or checkpoint kinase 2, which phosphorylate p53 at one of the three locations: Ser15, Thr18 or Ser20 (21). This causes an increase in the level of p53 and a parallel increase in MDM2 levels, which in turn regulates the total level of p53 protein via a regulatory loop (20). Following DNA damage repair, the ATM serine/threonine kinase is deactivated, resulting in rapid dephosphorylation and destruction of p53 by accumulated MDM2 (20).

3. *TP53* mutations in breast cancer

Somatic mutations in the *TP53* gene are one of the most common genetic abnormalities associated with human cancer. The frequency of *TP53* mutations reported in breast tumors ranges between 15-71% (22,23). Germline *TP53* mutations are associated with a predisposition to a wide spectrum of early-onset cancer: LFS and Li-Fraumeni-like syndromes (LFL) (24-26). *TP53* mutations were reported at a significantly higher frequency in patients with breast cancer and germline breast and ovarian cancer susceptibility protein 1 (*BRCA1)* and 2 (*BRCA2*) mutations (27,28). The most common *TP53* mutations are missense substitutions, which occur in 75% of cases. Other mutations observed in the *TP53* gene are frameshift insertions and deletions (9%), nonsense (7%) and silent mutations (5%) (29).

4. Germline *TP53* mutations

Germline *TP53* gene mutations increase the risk of a number of cancer types, including breast cancer, leukemia, soft tissue sarcomas, CNS tumors and adrenocortical cancer (as part of LFS) (30). LFS is an autosomal dominant inherited syndrome that predisposes to development of cancer in affected families. *TP53* mutations have been identified in patients with classic LFS (31), LFL (32) or incomplete LFS (33) and in groups of patients with certain cancer types or with multiple tumors (34).

The criteria for classic LFS are as follows: A patient with sarcoma diagnosed at <45 years old; a first-degree relative (a parent, sibling or child) with cancer diagnosed at <45 years old; and an additional first- or second-degree relative (a grandparent, aunt/uncle, niece/nephew or grandchild) with cancer diagnosed at <45 years old or a sarcoma diagnosed at any age (31). In clinical practice, the Chompret criteria are also employed, which helps to identify families with LFS who do not necessarily meet the classic criteria. A diagnosis of LFS can be considered for a patient with a personal and family history that meets 1 of the 3 Chompret criteria (35) (Table I). Other criteria for the diagnosis of LFL have also been described in the literature. The details of the Birch criteria are as follows: A patient with any childhood cancer or sarcoma, brain tumor or adrenocortical carcinoma diagnosed at <45 years old; a first- or second-degree relative with a typical Li-Fraumeni cancer (sarcoma, breast cancer, brain tumor, adrenocortical carcinoma or leukemia) at any age; and a first- or second-degree relative with any cancer at <60 years old (32). However, LFS (one in 5,000-20,000 individuals) and LFL are rare (36).

The most frequent cancer types observed in carriers of *TP53* mutations were breast cancer, soft tissue and bone sarcoma (>50% of tumors), followed by adrenocortical carcinomas and brain tumors (31,37). Other cancer types, including hematological, gastric, colorectal and ovarian cancer, occur earlier in *TP53* mutations carriers than in the general population (38). Certain cancer types are observed more rarely than others in *TP53* germline mutation carriers, including choroid plexus carcinoma and papilloma (at <15 years old), Wilms' tumor and malignant phyllodes tumors (37).

Table I. Chompret criteria for clinical diagnosis of LFS.

Criteria	Description
1	• Presence of a tumor belonging to the LFS tumor spectrum (<46 years old) • ≥1 first- • or second-degree family member with a tumor in the LFS tumor spectrum (<56 years old) or with multiple tumors
2	• Presence of multiple tumors (non-breast) • Presence of 2 tumors that belong to the LFS tumor spectrum • Occurrence of the first tumor in the LFS tumor spectrum at <46 years old
3	• Presence of adrenal cortical carcinoma or a tumor in the choroid plexus, regardless of family history.

LFS, Li-Fraumeni syndrome.

A total of >250 germline mutations in the *TP53* gene have been described (39,40), and the most common germline mutations are missense mutations (77%). The first mutations that were analyzed were within exons 5-8, which are responsible for encoding the DNA-binding domain of the protein (37,38). Mutations have also been reported outside of the DNA-binding domain. Assumpção *et al* (41) demonstrated that the *TP53 R337H* mutation might significantly increase the risk of breast cancer in carriers (P=0.0442).

5. Somatic *TP53* mutations

Somatic *TP53* gene mutations are present in the majority of human cancer types (6). The most common *TP53* mutations are missense substitutions, which occur in 75% of cases. Other alterations include frameshift insertions and deletions (9%), nonsense mutations (7%), silent mutations (5%) and other infrequent mutations (6). Around 30% cancer-associated TP53 missense mutations are nucleotide substitutions at highly mutable CpG dinucleotides, at codons encoding regions essential for the contact between the p53 protein and specific DNA sequences (24). These mutations are associated with the loss of DNA binding activity and transactivation capacity (24). A total of 34 missense mutations that result from transitions at CpG sites within exons 5-8 have been identified (42). Proteins encoded by the mutated *TP53* gene may interfere with wild-type p53 and form hetero-oligomers with a reduced capacity for DNA binding (43).

The value of the *TP53* mutation status for predicting tumor response to treatment and patient outcome has been evaluated in numerous cancer types, including breast cancer. The majority of the studies, including large-cohort studies, have demonstrated that *TP53* mutations were associated with a poorer prognosis (6,44). The missense and non-missense mutations have a similar prognostic value (reduced outcome) (6). Olivier *et al* (6) analyzed the clinical value of *TP53* somatic mutations in primary breast cancer. In the study, *TP53* mutations were most frequent in ductal and medullar cancer with aggressive phenotypes (high histological grade, large size, lymph node metastasis and low hormone receptor expression) and in patients <60 years old (6). *TP53* mutations within exons 5-8 were associated with an elevated risk of mortality (2.27-fold) in patients with breast cancer (relative risk >10 years; P<0.0001), compared with patients without mutations. The combination of *TP53* mutation and negative progesterone receptor status was associated with worse prognosis. The presence of missense mutations (codon 179 and R248W) may also be associated with a reduced prognosis (43). Certain differences in prognosis have been observed in patients with missense mutations located outside the DNA-binding sites and those with missense mutations located within the DNA-binding sites (6). However, the mechanism underlying this remains unknown. In a large study, *TP53* mutations status was revealed to be a risk factor of disease recurrence and mortality in lymph node-negative patients with HER-2-positive tumors (45). In a subsequent trial, the frequency of *TP53* mutations was higher in node-positive breast cancer and in tumors that were characterized as invasive ductal carcinoma and of a larger size or with negative steroid receptor status (46). In the univariate analysis, disease-free survival time and overall survival (OS) time were associated with tumor size, lymph node status, histologic degree of anaplasia, steroid receptor status and presence of *TP53* mutations (46). In another study, the *TP53* mutation status was revealed to be associated with basal-like breast cancer, which characterized by the absence of estrogen receptor α expression, progesterone receptor, HER2 or 'luminal' cytokeratins (CK8/18/19), higher mitotic index and Ki-67 (47).

The role of *TP53* mutations as predictive factors has been reported in various types of cancer, including breast cancer. Andersson *et al* (48) demonstrated that *TP53* mutation status was a significant prognostic factor for relapse-free survival time (RFS), breast cancer-corrected survival (BCCS) time and OS time in a group of patients who had received adjuvant cyclophosphamide, methotrexate and 5-fluorouracil (CMF)-based regimens. A poorer overall survival time (OS) for *TP53* mutation carriers was also observed in patients treated with CMF (P=0.001). The *TP53* mutation status was also a prognostic factor of borderline significance with regards to BCCS time (P=0.05) in patients with estrogen receptor-positive status tumors who had received tamoxifen. However, *TP53* mutation status was not a significant prognostic indicator of RFS time or OS time in the same group of patients (48). Certain studies have reported that the *TP53* mutation status was not a prognostic factor of survival in patients who had received tamoxifen therapy (49,50).

Furthermore, Bergh *et al* (51) revealed that adjuvant systemic therapies, including radiotherapy and hormone therapy with tamoxifen, were less effective in patients with *TP53* mutations and positive lymph nodes. In other studies, *TP53* status has been reported to be a predictive indicator of a poor response to tamoxifen in metastatic disease and a prognostic factor indicator of reduced survival rate following adjuvant therapy with tamoxifen (52,53). Certain preliminary results have reported an association between *TP53* mutations and a reduced response to the fluorouracil, Adriamycin and cytoxan chemotherapy regimen (54). In multivariate analysis, patient age, menopause status, disease-free interval, steroid receptor status (estrogen and progesterone) and presence of *TP53* mutation were predictive indicators of a poor response to treatment in a tamoxifen-treated group (P=0.0014). The median PFS time following chemotherapy was reduced for patients with a *TP53* mutation compared with those with wild-type *TP53* (6.6 and 0.6 months, respectively) (52).

TP53 mutations have been revealed to be associated with an advanced and aggressive tumor phenotype (genomic instability, high mitotic frequency, higher Ki-67 expression and high cyclin E expression). Associations were also reported between *TP53* mutations and tumors with larger size, higher disease grade, lymph node metastases and negative estrogen and progesterone receptor status (55,56).

Martinez Bueno *et al* (57) analyzed data from a phase II trial that compared olaparib [an inhibitor of poly ADP ribose polymerase (PARP)] with a placebo. The patients with *TP53* mutations exhibited a statistically significant improvement in OS following the use of olaparib compared with non-carriers (18 and 7.5 months, respectively). In patients with wild-type *BRCA* genes, only *TP53* mutation carriers have been revealed to achieve an improved OS with olaparib (57).

6. *TP53* polymorphisms in breast cancer

An SNP is defined as a single nucleotide change in a DNA sequence that occurs in >1% of the population (15). A SNP is the most common type of change in DNA (15), and the number of SNPs has been systematically identified. However, the clinical consequences of the majority of SNPs remain unknown.

The most frequently reported SNP (SNP72; rs1042522) is a G/C variation at the second position of codon 72 in exon 4, leading to Arg72 or Pro72 protein variants, which serve roles in numerous types of cancer (58). The frequency of SNP72 has been demonstrated to vary among Caucasian, Chinese and African-American patients. The Arg72 variant is more common in Caucasian patients, whilst the Pro72 variant is more frequently detected in Chinese and African-American patients (59,60). Pro72 is located within a proline-rich region and may cause changes in the structure of the SH3-binding domain in the p53 protein. The Pro72 variant induces cell-cycle arrest and DNA repair (61,62). It has also been reported that Arg72 variant is more efficient at inducing apoptosis due to its greater ability to interact with MDM2 than the Pro72 variant (63). In certain studies, polymorphisms in *MDM2* and *AKT1*, which regulate the *TP53* pathway, may modify the functions of *TP53* (64,65).

Toyama *et al* (66) reported that the Pro/Pro genotype of *TP53* codon 72 may be an independent prognostic factor for patients with breast cancer. In the study, the Pro/Pro genotype was associated with a reduced disease free survival (DFS) compared with other genotypes (P=0.049), particularly in the subgroup of patients who were treated with adjuvant chemotherapy (P=0.009). By contrast, in the subgroup of patients treated with adjuvant hormonal therapy or without adjuvant systemic treatment, 72 genotype variants were not associated with DFS.

Another polymorphism (rs2279744; '-410T-G; SNP309; SNP309T>G) is a variant in the promoter of *MDM2*. The GG genotype of the rs2279744 polymorphism was associated with the presence of high-grade breast tumors and lymph node metastasis (P=0.009) (67). In another analysis, a SNP in the promoter of *MDM2* was associated with the development of LFS at an earlier age and the presence of sporadic cancer (68). The other reported polymorphisms include intron 3 duplication (rs17878362), which has been associated with increased cancer susceptibility, (69) intron 4 SNP (rs1794287) (70) and P47S (rs1800371), which has been associated with apoptosis (71).

7. Guidelines for examination and screening of patients with *TP53* mutations

The National Comprehensive Cancer Network (NCCN) guidelines for females with LFS and *TP53* mutations include breast self-examination from the age of 18, clinical breast examination every 6-12 months from the age of 20-25 and breast magnetic resonance imaging (MRI) or mammogram from the age of 30 (68). Additionally, the NCCN recommends annual breast MRI with contrast or mammogram from the age of 20 or when breast cancer is diagnosed in cases with a family history of breast cancer prior to the age of 20. Breast cancer examination should start at the age of 18 (67). Annual mammograms and MRI screenings should be performed between 30-75 years (16). Screening of patients >75 years old should be based on individual assessment. Patients of both genders with LFS should have annual physical examinations, skin cancer screenings, brain MRIs and colonoscopies every 2-5 years from the age of 25. Whole body MRIs should also be considered (68). The family history of cancer is also very important and should be recorded. In families with *TP53* mutations, the risk of childhood cancer should be assessed (68). The NCCN guidelines recommend testing for *TP53* mutations in females with breast cancer diagnosis and are <35 years old and without *BRCA1*/*BRCA2* mutations. In clinical practice, the NCCN guidelines recommend the option of a risk-reducing mastectomy following discussion regarding *TP53* mutations (68). Therapeutic radiotherapy should be used with caution in patients with *TP53* mutations due to increased sensitivity to radiation. Breast cancer is the most common tumor type observed in patients with germline *TP53* mutations (16).

The National Institute of Clinical Excellence guidelines recommend MRI as a basic examination for female carriers of *TP53* mutations that are aged between 20-50 years with a family history of breast cancer (72). Annual mammography for patients >50 years old is also recommended (72). Furthermore, the Institute of Cancer Research protocol advises self-examination of breast and annual MRI between the ages of 20-50 years. In addition, it is recommended that

a review should be undertaken at age 50, and a discussion of risk-reducing mastectomy in *TP53* mutation carriers (73).

8. Conclusions

Germline mutations in *TP53* are associated with a higher risk of breast cancer that is observed in patients with LFS. The presence of *TP53* mutations increases the risk of developing certain cancer types (including breast cancer) at a younger age (~30 years) and general lifetime cancer risk. Breast cancer is the most frequently observed tumor type in patients with germline mutations. In a previous study, there was a high frequency of somatic *TP53* mutations in patients with a basal-like breast cancer and HER-2-positive tumors or estrogen receptor-negative tumors (9,68). Furthermore, a number of studies have indicated the role of the *TP53* mutation as a prognostic factor for the success of chemotherapy, hormonotherapy (in breast cancer) and PARP inhibitors (including olaparib for the treatment of ovarian cancer).

Practice recommendations regarding risk assessment, genetic counseling, breast cancer screening and clinical procedures in *TP53* mutation carriers are outlined in the NCCN guidelines for hereditary breast and ovarian cancer. The presence of *TP53* mutations may have clinical implications, including decisions on performing mastectomies or therapeutic radiotherapy. In breast cancer, *TP53* mutations are an independent marker of a poorer OS time. The role of *TP53* mutations and SNPs as predictive factors for the success of chemotherapy and radiotherapy remain under investigation with no clinical indication having been identified thus far.

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Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interest.

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