

Original Article



Clinical Features of Breast Cancer in South Korean Patients with Germline *TP53* Gene Mutations

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ABSTRACT



Purpose: Li-Fraumeni syndrome (LFS) is a rare autosomal cancer syndrome caused by a germline mutation in the *TP53* gene. Breast cancer in LFS patients is of various subtypes; however, limited data are available on the clinicopathological features of these subtypes and their appropriate treatments. This study aimed to review the clinical features and treatments for breast cancer in South Korean patients with germline *TP53* mutations.

Methods: Data on the clinicopathological features and treatment of all breast cancer patients with LFS were collected retrospectively from the available database of 4 tertiary hospitals in the Republic of Korea.

Results: Twenty-one breast cancer cases in 12 unrelated women with confirmed germline *TP53* mutations were included in the study. The median age at diagnosis was 33.5 years. The histopathological diagnosis included invasive ductal carcinoma (n = 16), ductal carcinoma *in situ* (n = 3), and malignant phyllodes tumor (n = 2). While 42% and 31% of the cases were positive for estrogen and progesterone receptors, respectively, 52.6% were human epidermal growth factor receptor 2 (HER2) positive, and 21% were triple-negative. The treatments included mastectomy (52%) and breast-conserving surgery (38%). Five patients underwent radiotherapy (RT). The median follow-up period was 87.5 (8–222) months. There were 3 ipsilateral and 4 contralateral breast recurrences during the follow-up, and 8 patients developed new primary cancers. In the post-RT subgroup, there were 2 ipsilateral and 2 contralateral breast recurrences in 1 patient, and 4 patients had a new primary cancer.

Conclusion: As reported in other countries, breast cancer in LFS patients in South Korea had an early onset and were predominantly but not exclusively positive for HER2. A multidisciplinary approach with adherence to the treatment guidelines, considering mastectomy, and avoiding RT is encouraged to prevent RT-associated sequelae in LFS patients.

Keywords: Breast neoplasms; Genes, erbB-2; Li-Fraumeni syndrome; Genes, p53

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Conflict of Interest

The authors declare that they have no competing interests. Han-Byoel Lee is a member of the board of directors of, and has stock and ownership interests at DCGen, Co., Ltd., outside the submitted work.

Author Contributions

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INTRODUCTION

Of all breast cancers, 5%–10% are hereditary. *BRCA1/BRCA2* mutations are the most common mutations identified in families with a high risk of breast cancer [1]. Other genes associated with hereditary susceptibility to breast cancer and varying penetrance levels include *CDH1*, *CHEK2*, *PALB2*, *ATM*, *PTEN*, and *TP53* [2-5]. Li-Fraumeni syndrome (LFS) is a rare autosomal dominant familial cancer syndrome caused by a germline mutation in the *TP53* gene and is involved in about 1% of hereditary breast cancers [6]. *TP53* is a tumor suppressor gene that plays a vital role in cell cycle control, apoptosis, and DNA repair. Germline *TP53* mutation is associated with a broad spectrum of tumors, including soft tissue sarcoma, breast, brain, lung, and adrenocortical cancers. Early onset breast cancer is the most common feature in patients with LFS, with a lifetime risk greater than 60% [7].

In the last two decades, with the increasing availability of genetic testing, hereditary breast cancers have become more common. However, there is limited data on the clinical features and treatment for some types of breast cancers, such as those in patients with germline *TP53* gene mutations. Approaching such patients requires a multidisciplinary team with up-to-date knowledge of the disease features and proper treatments.

A few reports have stated that LFS-associated breast cancers are most commonly of a high histological grade and are positive for estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) [8]. We retrospectively gathered data from tertiary hospitals in the Republic of Korea to describe the clinicopathological features and breast cancer treatment in patients with LFS.

METHODS

This study was approved by the Institutional Review Boards of the participating hospitals. We retrospectively collected data from 4 tertiary hospitals in the Republic of Korea (Seoul St. Mary's Hospital KC20RIDI0311, Gangnam Severance Hospital 3-2020-0234, Seoul National University Hospital 1507-132-689, and Samsung Medical Center 2020-06-077) on all patients diagnosed with breast cancer between January 2005 and December 2019. The requirement for informed consent was waived due to the retrospective nature of the study. The included patients had a confirmed germline *TP53* mutation based on the classic or Chompret criteria for LFS (**Supplementary Table 1**) [9] or had a personal history of breast cancer at a younger age and did not have an identifiable mutation in *BRCA1/2* genes. Germline *TP53* mutations were confirmed by Sanger or next-generation sequencing (NGS). The reading criteria for the pathology results were hospital-based.

Clinical information including the patient's age at diagnosis, personal and family history of cancer, mutation status, histopathological features including histological grade, hormonal receptors, *HER2* status, type of surgical treatment, chemotherapy, radiotherapy (RT), and hormonal therapy was collected from the available medical records and analyzed.

RESULTS

The clinicopathological features, treatments, and follow-up data of the study participants are summarized in **Table 1**.

Table 1. Clinicopathological features, treatment, and follow-up data of breast cancer patients with germline TP53 mutations

Case	Age at diagnosis (yr)	Side	Breast cancer type	Grade	ER	PR	HER2	Surgery	Chemotherapy	RT	HRT	Anti-HER2 therapy	TP53 mutation	Follow-up (mon)*	Other cancers	Family history
1	31	Right	IDC	High	Neg	Neg	Pos	Mastectomy	Yes	No	Yes	Yes	Missense	9	None	Father: lung cancer Brother: osteosarcoma
2	25	Left	DCIS	High	Pos	Pos	Neg	Mastectomy								Mother: leukemia Grandmother: breast cancer
3	47	Right	IDC	Intermediate	Neg	Neg	Pos	BCS	Yes	Yes	No	No	Missense	96	None	Father: esophageal cancer Brother: lung cancer
4†	28-30	Left	IDC	High	Neg	Neg	Pos	Mastectomy	Yes	NA	NA	NA	Frameshift	222	- Nasal cavity squamous cancer - Lung cancer	Daughter: ovarian cancer
5†	37-39	Right	IDC	Intermediate	Pos	Pos	Pos	Mastectomy	Yes	No	Yes	Yes			- Thyroid cancer	Father: cancer unknown site
	19-21	Left	Malignant phyllodes	Intermediate	NA	NA	NA	Wide excision	NA	NA	NA	NA	Missense	79	- Chondrosarcoma nasal cavity - Marginal zone B-cell lymphoma, conjunctiva - MALoma, extranodal, Rt maxillary	
	28-30	Right	IDC	Intermediate	Pos	Pos	Neg	Mastectomy	No	No	Yes	No			- Colon cancer - Lung cancer - Stomach cancer	Brother: stomach cancer
6†	46-48	Left	IDC	High	Neg	Neg	Pos	Mastectomy	Yes	NA	NA	NA	Missense	120	- Lung cancer - Stomach cancer	Brother: stomach cancer
	55-57	Right	IDC	High	Neg	Neg	Neg	Mastectomy	Yes	No	No	No			Lung cancer	Unknown
7	41	Right	IDC	High	Neg	Neg	Pos	Mastectomy	Yes	No	No	Yes	Missense	144	Lung cancer	Father: liver cancer
8	48	Right	IDC	Intermediate	Pos	Pos	Pos	BCS	Yes	Yes	Yes	No	Missense	124	Pre-B ALL	None
9‡	34	Left	IDC	Intermediate	Pos	Neg	Pos	Mastectomy	Yes	No	Yes	No	Missense	8	Bone metastasis	None
10	52	Left	IDC	Intermediate	Pos	Pos	Neg	BCS	Yes	Yes	Yes	No	Missense	40	Thyroid cancer	2 Sisters: breast cancer 1 Sister: ovarian cancer
11	20	Left	Malignant phyllodes	Unknown	NA	NA	NA	Wide excision	NA	NA	NA	NA	Missense	156	Lung cancer	None
		Left	IDC	Unknown	Neg	Neg	Pos	BCS	Yes	Yes	No	No				None
	28	Left	IDC	Intermediate	Neg	Neg	Neg	BCS	Yes	No	Yes	No				None
		Right	DCIS	High	Neg	Neg	Pos	BCS	No	Yes	No	No				None
	29	Right	DCIS	High	Pos	Neg	Neg	BCS	No	No	Yes	No				None
	32	Left	IDC	High	Neg	Neg	Neg	Mastectomy	Yes	No	No	No				None
12	33	Left	IDC	Unknown	Pos	Neg	Neg	Mastectomy	Yes	Yes	Yes	No	Synonymous	31	Thymoma	None

IDC, invasive ductal carcinoma; DCIS, ductal carcinoma in situ; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor; BCS, breast-conserving surgery; NA, not applicable; ALL, acute lymphoblastic lymphoma; RT, radiotherapy; HRT, hormone therapy; Pos, positive; Neg, negative.

*Follow-up started after the first breast cancer diagnosis; †Age range was recommended by the hospital Ethics Committee for more privacy; ‡Patient expired.

Demographic data

Twelve unrelated women with confirmed germline *TP53* mutations were diagnosed with 21 breast cancers. The median age at initial diagnosis was 33.5 (20–52) years. Five women had bilateral breast cancer, 4 had metachronous contralateral breast cancer, and 1 patient had synchronous breast cancer.

Histopathological data

The histopathological diagnosis included invasive ductal carcinoma (IDC) (n = 16), ductal carcinoma *in situ* (DCIS) (n = 3), and malignant phyllodes tumor (n = 2). Of the cases with IDC and DCIS, 50% had high or intermediate histological grades. Additionally, 8 (42%) and 6 (31%) cases were positive for ER and progesterone receptor (PR), respectively. While 10 (52.6%) cases were HER2 positive (immunohistochemistry 3+ or fluorescence in situ hybridization amplified), 4 (21%) were triple-negative. Malignant phyllodes tumors were the initial presentation in 2 patients, and both developed IDC later.

Treatment

Of all cases, 52% and 38% were treated with mastectomy and breast-conserving surgery (BCS), respectively, and 10% had only wide excision of the malignant phyllodes tumor. Chemotherapy was administered to 11 patients, 3 of whom were treated twice or more for recurrence in the ipsilateral or contralateral breast. Five patients received RT to treat 6 breast cancers following BCS in 5 cases and mastectomy in 1 case. All patients with hormone receptor-positive cancers were treated with tamoxifen, and 57% of the HER2-positive patients received targeted therapy, mainly trastuzumab. The median follow-up period was 87.5 (8–222) months from the first breast cancer diagnosis. There were 3 cases of ipsilateral and 4 cases of contralateral breast cancer recurrences during the follow-up period, and 8 patients developed new primary cancers. The left breast cancer in patient 11 (**Table 1**) was treated with BCS and RT. Subsequently, she developed bilateral recurrence, which was treated with bilateral BCS and right-side RT. She also had right breast recurrence, which was treated with BCS, and finally had left breast recurrence, for which she underwent mastectomy. Only 1 patient had a distant metastasis and died 8 months after diagnosis of breast cancer (case 9, bone metastasis). In the follow-up data of the post-RT subgroup, there were 2 ipsilateral and 2 contralateral breast cancer recurrences in 1 patient who had bilateral breast RT. The other 4 patients who underwent adjuvant RT had no locoregional recurrence for a median follow-up duration of 68 months (range, 31–124 months). Four patients developed new primary cancers, including acute lymphoblastic lymphoma, lung cancer, thyroid cancer, and thymoma.

Li-Fraumeni syndrome and *TP53* mutation type

The *TP53* mutation types, testing methods, and indications are shown in **Table 2**. Testing for *TP53* mutation was based on suspected personal and/or family history as per the classic or Chompret criteria for LFS. Two patients diagnosed with breast cancer at a younger age with no identifiable *BRCA1/2* gene mutations were subsequently tested for *TP53* mutation by using a multigene panel NGS. Ten patients had a missense variant, one had a frameshift, and the other had a synonymous mutation.

Nine (75%) patients had a personal history of one or more additional primary malignancies (lymphoma/MALToma, n = 3; lung cancer, n = 4; thyroid cancer, n = 2; chondrosarcoma, n = 1; nasal squamous carcinoma, n = 1; skin cancer, n = 1; colon cancer, n = 1; stomach cancer, n = 1; pancreatic cancer, n = 1; and thymoma, n = 1), which are considered core components or high-risk associated cancers of LFS. Two patients had childhood malignancies before breast cancer. Eight (67%) patients reported a family history (mostly a first-degree relative) of different types of cancer, including (breast

Table 2. *TP53* gene mutation types, testing methods, and indications in patients with breast cancer in South Korea

Case	Hospital	Testing method	Indication	<i>TP53</i> mutation		
				NT alteration	AA alteration	Mutation type
1	Seoul St. Mary's Hospital	Multigene panel NGS	Brother was diagnosed with LFS at another hospital after been diagnosed with sarcoma	c.743G>A	P.Arg248Gln	Missense
2	Seoul St. Mary's Hospital	Multigene panel NGS	Young age at diagnosis of breast cancer (25) with negative <i>BRCA</i> gene test	c.824G>A	P.Cys275Tyr	Missense
3	Samsung Medical center	Sanger sequencing	Comprehensively applying classic criteria and Chompret criteria of LFS. The reason for applying both criteria is because the sensitivity and specificity of the criteria are different	c.78delT	P.Pro27Leu17	Frameshift
4	Samsung Medical center	Sanger sequencing	Comprehensively applying classic criteria and Chompret criteria of LFS. The reason for applying both criteria is because the sensitivity and specificity of the criteria are different	c.742C>T	P.Arg248Trp	Missense
5	Samsung Medical center	Sanger sequencing	Comprehensively applying classic criteria and Chompret criteria of LFS. The reason for applying both criteria is because the sensitivity and specificity of the criteria are different	c.590T>G	P.Val197Gly	Missense
6	Gangnam Severance Hospital	Sanger sequencing	Suspected due to the family history (father: esophageal cancer, brother: lung cancer)	c.566C>T	P.Ala189Val	Missense
7	SNUH	Unknown	Done at another hospital	c.743G>A	P.Arg248Gln	Missense
8	SNUH	Multigene panel NGS	Young age at diagnosis of breast cancer (35) with negative <i>BRCA</i> gene test	c.730G>A	P.Gly244Ser	Missense
9	SNUH	Multigene panel NGS	Due to multiple primary tumors in one patient (lung cancer)	c.542G>A	P.Arg181His	Missense
10	SNUH	Multigene panel NGS	Screening	c.638G>A	P.Arg213Gln	Missense
11	SNUH	Multigene panel NGS	Suspected due to hematological malignancies (leukemia)	c.524G>A	P.Arg175His	Missense
12	SNUH	Sanger sequencing	Presence of multiple cancers (thymoma) with negative <i>BRCA</i> gene test	c.375G>A	p.Thr125=	Synonymous

SNUH, Seoul National University Hospital; NGS, next-generation sequencing; LFS, Li-Fraumeni syndrome; NT, nucleotide; AA, amino acid.

cancer, n = 3; lung cancer, n = 2; ovarian cancer, n = 2; osteosarcoma, n = 1; leukemia, n = 1; stomach cancer, n = 1; pancreatic cancer, n = 1; liver cancer, n = 1; and esophageal cancer, n = 1).

DISCUSSION

In women with LFS, breast cancer is the most common malignancy (79%), followed by soft tissue sarcoma (27%) [10]. The cumulative breast cancer incidence in LFS patients is approximately 85% by the age of 60, a risk level comparable to that seen in patients with *BRCA1* and *BRCA2* germline mutations. The annual hazard rate of breast cancer in these patients increases in the late teens (age 18–20 years) and peaks at about age 40 [11]. In our study, the median age of LFS patients with breast cancer was 33.5 (20–52) years, which is considered as early onset when compared to the age of onset in the general Korean population (40–49 years) [12].

In hereditary breast cancer, the subtypes differ based on hereditary predisposing syndrome. While breast cancers in individuals with *BRCA1* mutations are predominantly triple negative breast cancer, 80% of them in *BRCA2* mutation carriers are ER positive and HER2 negative. Women with *CDH1* mutations have invasive lobular breast tumors [13]. Breast cancers in individuals with germline *TP53* mutations (LFS) are predominantly ER and/or HER2 positive [8].

In our review of 21 tumors in 12 women with *TP53* mutations, 52.6% (10 out of 19) of the tumors were HER2 positive, and 42% were ER or PR positive. Generally, in invasive breast cancer, the *HER2* gene is amplified in 15%–25% of cases [14]. Our results confirm that breast cancers in LFS patients are predominantly HER2 positive.

A few studies have described the histopathological features of breast cancer in patients with LFS. In a study of early onset breast cancer, Wilson et al. [15] found that HER2 was amplified in 83% of LFS patients compared to 16% in the control group. A retrospective study from the MD Anderson Cancer Center including 30 breast cancers in women with *TP53* mutations confirmed these findings with HER2 overexpression in 67% and ER positivity in 70% of the tumors compared to 25% HER2 positivity and 68% ER positivity in the control group of *TP53* mutation-negative patients [16]. In a larger study of 39 LFS patients who had 43 breast cancers (32 invasive and 11 DCIS), Masciari et al. [8] found HER2 amplification in 63% of invasive and 73% of DCIS cancers.

Two patients in our study initially presented with malignant phyllodes tumors. The incidence of adrenocortical cancer and malignant phyllodes showed the greatest increase in patients with *TP53* mutations relative to the general population [17]. In a study conducted to determine the incidence of germline genetic mutations in 550 patients with phyllodes tumors, almost 10% of the patients who tested positive for a germline cancer predisposition gene (*BRCA1/2*, *TP53*) carried a deleterious mutation. The authors suggested including phyllodes tumors in the criteria for genetic counseling and testing for known heritable cancer syndromes since they may have been the presenting tumors in these young women. Additionally, they may represent a *de novo* mutation, which cannot be predicted based on their family history alone [18]. These tumors are currently not included in the National Comprehensive Cancer Network practice guidelines as criteria for genetic counseling or testing for any known heritable cancer syndromes. Further studies with large samples are needed to confirm the relationship between these mutations and phyllodes tumors before changing the current recommendation.

An analysis of the *TP53* database by the International Agency for Research on Cancer showed that of all cancers caused by *TP53* mutations, missense mutations account for more than 70% of the cases, followed by nonsense and splice mutations [19]. In our study, the most common mutation was a missense mutation. HER2 amplification was observed in all mutation types.

The treatment of breast cancer in patients with LFS follows the same principles as in sporadic cancer, except for RT, which is contraindicated in these patients to avoid radiation-associated sequelae. The recently published *American Society of Clinical Oncology* guidelines for the management of hereditary breast cancers state that irradiation of intact breasts is contraindicated in women carrying a germline *TP53* mutation. In these cases, mastectomy is the recommended therapeutic option, and post-mastectomy RT should only be considered in patients with a significant risk of locoregional recurrence [20]. It is expected that the carriers of a *TP53* mutation would be unable to repair tissue damage from DNA-damaging RT, thereby significantly increasing the risk for RT-associated sequelae [21].

The follow-up data of the 5 patients who underwent adjuvant RT in our study showed 4 patients with a new primary cancer (acute lymphoblastic lymphoma, lung cancer, thyroid cancer, and thymoma) that were not regarded to be related to RT. Only 1 patient had 2 ipsilateral and 2 contralateral breast cancer recurrences after breast RT. These recurrences and primaries are probably the net effect of genetic predisposition on both the risk of new primaries and RT-associated cancers. A single case series by Heymann et al. [22] studied the clinical outcomes in 6 patients with germline *TP53* mutations who had received RT after breast cancer surgery. There were 3 contralateral breast cancer recurrences, 3 ipsilateral breast cancer recurrences, 2 RT-induced cancers, and 3 new primary cancers. Based on these observations, mastectomy of the breast bearing the cancer and a contralateral prophylactic

mastectomy were advised. However, other studies have suggested that RT does not always result in additional malignancies in LFS patients [23]. Le et al. [24] found that only 2 patients had radiation-induced malignancies (thyroid and sarcoma), and only 1 had a locoregional recurrence among the 18 LFS patients with breast cancer who were treated with RT. These findings showed that LFS does not have to be an absolute contraindication for RT in breast cancer. However, future studies with longer follow-up periods and larger sample sizes are needed before making changes to the current recommendations.

The limitations of our study are its retrospective nature and small sample size. However, to the best of our knowledge, by reviewing the published data so far, this is the only study describing the histopathological features and management of breast cancer patients with *TP53* mutations in an Asian population.

In conclusion, breast cancer in LFS patients in South Korea had an early onset and were predominantly but not exclusively HER2 positive. A multidisciplinary approach with adherence to the treatment guidelines, considering mastectomy, and avoiding RT is encouraged to prevent RT-associated sequelae in LFS patients.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

The classical and Chompret criteria for the diagnosis of LFS [9]

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