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ARTICLE

Histopathologic features of breast cancer in Li–Fraumeni syndrome

M. Gabriela Kuba[1,2] · Susan C. Lester[1] · Teresa Bowman[1] · Samantha M. Stokes[3] · Krishan L. Taneja[1] · Judy E. Garber[3] · Deborah A. Dillon[1]

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Abstract

Breast cancer is the most common malignancy in female patients with Li–Fraumeni syndrome (LFS), a rare autosomal dominant hereditary syndrome characterized by germline *TP53* mutations. Recent studies have shown that the majority of these tumors are estrogen receptor (ER) positive with frequent HER2 co-expression. However, the morphologic features of these tumors have not been as well studied as other germline-associated breast cancers. We evaluated the pathologic features of 27 invasive and in situ carcinomas from patients with known germline *TP53* mutations collected through the Li–Fraumeni Consortium. Overall, 60% of cases were HER2 positive and 44% showed ER co-expression. Most DCIS was high nuclear grade with central necrosis and associated periductal fibrosis and lymphocytic response. Invasive carcinomas were mostly of ductal type (NOS), modified Scarff–Bloom–Richardson (mSBR) high grade, with marked nuclear atypia and high mitotic rate. Prominent tumor infiltrating lymphocytes, syncytial growth pattern, or pushing borders were not seen in these tumors. High p53 IHC expression was seen in tumors from individuals with germline *TP53* missense mutations whereas little or no protein expression (<1% nuclear expression, null pattern) was seen in tumors from carriers of non-missense mutations. In this study, we report in detail the morphologic features of invasive and in situ carcinomas in LFS. We found that these tumors share features with cancers harboring somatic *TP53* mutations but are distinct from *BRCA*-associated breast cancers.

Introduction

Breast cancer is the most common tumor among female patients with Li–Fraumeni syndrome (LFS) [1], a rare autosomal dominant hereditary syndrome characterized by germline *TP53* mutations. Breast cancer affects women with LFS at a much younger age compared to the general population in the United States (median age at diagnosis 32 vs 61 years) [2, 3]. It is estimated that 3–8% of women diagnosed with breast cancer under the age of 30 carry a germline *TP53* mutation [4]. The vast majority of *TP53* germline mutations identified in LFS are highly penetrant [5], with a cumulative incidence of breast cancer in women of 85% by age 60 [6].

The immunophenotypic profile of LFS-associated breast cancers has been recently described, showing these tumors to be significantly associated with HER2 amplification and overexpression (53–83%) [2, 7, 8]. Approximately 50% of cases co-express both estrogen receptor (ER) and HER2 [2, 7]. However, compared with other hereditary breast cancers [9, 10], relatively little is known about the histopathologic characteristics of breast cancer in LFS patients. In this study, we sought to describe the morphologic features of invasive and in situ carcinoma of the breast in patients with known germline *TP53* mutations.

Materials and methods

Eighteen cases of invasive mammary carcinoma and 9 cases of ductal carcinoma in situ (DCIS) from 25 patients with confirmed germline *TP53* mutations were identified through the LFS Consortium [11]. Two patients had two cancers each, which were considered separate primaries. One patient had bilateral cancer, with DCIS on the left breast and invasive

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✉ M. Gabriela Kuba
kubam@mskcc.org

[1] Department of Pathology, Brigham and Women's Hospital, Boston, MA, USA

[2] Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[3] Center for Cancer Genetics and Prevention, Dana-Farber Cancer Institute, Boston, MA, USA

ductal carcinoma (IDC) on the right side. The second patient had DCIS and IDC on the same breast but in different quadrants with different receptor profiles, and therefore considered as two separate primaries. The cases included in this study constituted a subset of those with available slides and tissue blocks from a cohort previously reported by the LFS Consortium [2]. Clinical data including age and stage at diagnosis and germline mutation status were previously collected under Dana Farber Cancer Institute IRB protocol #10-458.

Histologic analysis

Up to 3 representative H&E-stained sections from each case were reviewed. DCIS cases were evaluated for architecture, nuclear grade, presence of necrosis (central vs punctate), calcifications, periductal stromal/lymphocytic response, and apocrine features. Invasive carcinomas were classified by type (ductal, lobular, mixed ductal and lobular, or other special types), tubule score, nuclear grade, mitotic score, modified Scarff–Bloom–Richardson (mSBR) grade, presence of extensive necrosis (defined as >1 4x high-power field), pushing border (if slides from excision were available), syncytial growth pattern, apocrine features and stromal tumor infiltrating lymphocytes (TILs). Syncytial growth pattern was assigned when anastomosing sheets of tumor cells with indistinct cell borders were present, as in the initial descriptions of medullary carcinoma by Moore [12] and Ridolfi [13]. Apocrine features were defined as tumor cells with ample granular eosinophilic cytoplasm with enlarged, central nuclei and prominent nucleoli [1]. Carcinomas of mixed type or special types were classified according to WHO criteria [1]. Scoring of stromal TILs was performed using the recommendations of the International TILs Working Group [14].

Tissue microarray construction

A tissue microarray (TMA) was constructed in the Dana Farber/Harvard Cancer Center Tissue Microarray Core Facility as previously described [2]. Briefly, three 0.6 mm cores from invasive carcinomas and 4–6 0.6 mm cores from DCIS cases were taken from areas marked by a breast pathologist (DAD) and placed into a recipient block using a manual arrayer (Beecher Instruments).

Immunohistochemical studies

Immunohistochemistry (IHC) was performed on 4 µm tissue sections (TMA sections and whole slide sections if available) following pressure cooking antigen retrieval (Target Retrieval Solution pH 6.0, DAKO) using antibodies for ER (SP1, 1:40 dilution, Thermo Scientific), progesterone receptor (PR) (PgR 636, 1:50 dilution, DAKO), HER2 (SP3, 1:50 dilution, Thermo Scientific), and p53 (DO-7, 1:500 dilution, DAKO). EnVision plus system-HRP (DAKO) was used as the detection system for all antibodies. External positive and negative controls were included in each run.

Immunohistochemistry (IHC) scoring

Cases were scored as positive for ER and PR when there was ≥1% nuclear expression in tumor cells, according to 2010 ASCO/CAP guidelines [15]. IHC for HER2 was scored as positive 3+ (strong complete membrane immunoreactivity in >10% of tumor cells), equivocal 2+ (weak to moderate complete membrane staining in >10% of tumor cells), negative 1+ (faint, weak partial membrane staining in >10% of tumor cells), and negative 0 (no immunoreactivity or ≤10% tumor cells with faint incomplete staining) according to 2018 ASCO/CAP guidelines [16]. The antibody clone DO-7 used in this study recognizes both mutant and wild-type p53 protein. P53 expression was scored as percent positive nuclei in tumor cells.

Fluorescence in situ hybridization

Fluorescence in situ hybridization (FISH) was performed as previously described [2]. Hybridization signals were scored in at least 20 tumor cells for each case. Results were interpreted according to 2018 ASCO/CAP guidelines [16].

Results

Patient population

The median age at diagnosis was 31.5 and 34 years for invasive carcinoma and DCIS, respectively (Table 1). All patients were women who carried a germline *TP53* mutation. Specific type of mutation data was available for 23 of 25 patients. The majority were missense mutations (13/23), followed by nonsense mutations (6/23), deletions (2/23), and splice-site mutations (2/23).

Two DCIS cases also showed microinvasion. Additional clinical information on stage at diagnosis is summarized in Table 1.

Invasive carcinoma

Morphology

Seventeen cases (94%) of invasive carcinoma were of ductal type (Fig. 1). The remaining case showed mixed ductal and lobular features. The majority of cases were mSBR grade 3 (61%, Fig. 2a). Fourteen cases had a tubule score of 3 (78%), and 13 tumors were of high nuclear grade (72%). A mitotic score of 2 or 3 was seen in 39% of cases.

Only one case (6%) had apocrine features. None of the cases showed extensive tumor necrosis, pushing border, or syncytial growth pattern. Ten cases (56%) were associated with <10% stromal TILs. Only two cases (11%) had >50% stromal TILs.

Table 1 Cohort characteristics.

	DCIS ($n = 9$)[a,b]	Invasive carcinoma ($n = 18$)[b]
Median age at diagnosis (range)	34 (22–39)	31.5 (21–58)
Stage at diagnosis (TNM)		
Tis	7	–
Tmi	2	–
T1	–	9
T2	–	6
Tn/a	–	3
N0	6	7
N1	–	5
N2	–	0
N3	–	1
Nn/a	3	5

[a]Includes cases of DCIS with microinvasion.

[b]All patients were women.

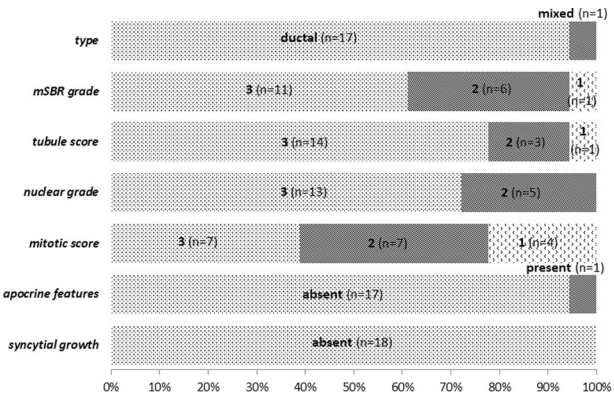

Fig. 1 Morphologic features of invasive carcinomas. The bar chart shows the distribution of histologic features of 18 invasive carcinomas.

Hormone receptor and HER2 Status

Seventeen cases had tissue available for IHC and/or FISH testing (Table 2). A total of nine cases were positive for HER2 (53%), all showing ER co-expression (Table 3). Mean ER expression in ER+/HER2+ cases was 58% (range 5–95%) compared to 92% in ER +/HER2− cases (range 80–95%) ($p = 0.023$, t-test). There were no ER-/PR + cases. Only two cases showed ER expression with negative PR results. Two cases were HER2 negative by IHC (1+) but positive by FISH. All remaining cases were HER2 concordant by IHC and FISH.

Ductal carcinoma in situ

Morphology

For the morphologic evaluation of DCIS, the *in situ* component of invasive tumors was also included in the analysis (n = 24, Fig. 3). DCIS cases showed a variety of architectural patterns; however, the most common predominant pattern was solid (15/24, 63%), followed by cribriform architecture (8/24, 33%). Twenty-two cases (92%) were of high nuclear grade (Fig. 4a). Central necrosis was present in 71% of cases (17/24). Associated calcifications and periductal fibrosis/lymphocytic response were seen in 58% (14/24) and 63% (15/24) of cases, respectively. Six cases (25%) showed apocrine features.

Hormone receptor and HER2 status

Eight cases had tissue available for IHC and/or FISH testing. DCIS was most frequently HER2+ (6/8, 75%), including two ER+/HER2+ cases. There were only two ER+/HER2− cases.

p53 immunohistochemistry

Of cases with available tissue for p53 IHC analysis, the majority of cases with missense mutations (9/13) showed

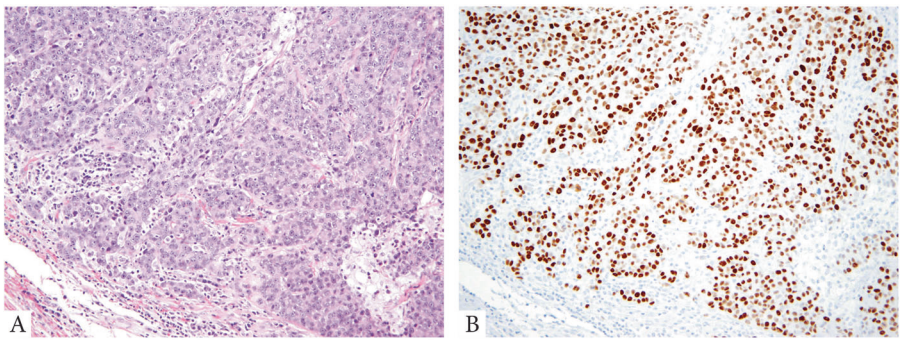

Fig. 2 Example of invasive carcinoma. Case 22: High-grade invasive ductal carcinoma (**a**) with p53 overexpression (**b**; mutant pattern) in a patient with a germline TP53 missense mutation.

Table 2 Hormone receptors, HER2 immunohistochemistry (IHC), and fluorescence in situ hybridization (FISH) results.

Case	Histology	ER (%)	PR (%)	HER2 IHC	HER2 FISH		
					Results	HER2 copy number	HER2/CEP17 ratio
1	DCIS	95	70	0	Negative	2.0	1.0
2	DCIS	95	30	0	Negative	2.0	1.1
3	DCIS	50	0	2+	Positive	7.9	2.7
4	DCIS mi	0	0	3+	Positive	21.6	12.7
5	DCIS	0	0	3+	Positive	19.1	10.6
6	DCIS	50	70	3+	Positive	7.9	4.5
7	DCIS	N/A	N/A	N/A	N/A	N/A	N/A
8	DCIS mi	0	0	3+	Positive	10.8	2.7
9	DCIS	0	0	3+	N/A	N/A	N/A
10	IDC	90	40	0	N/A	N/A	N/A
11	IDC	95	70	1+	Positive	4.9	2.3
12	IDC	10	1	3+	Positive	15.7	8.1
13	IDC	95	25	3+	N/A	N/A	N/A
14	IDC	80	10	0	Negative	N/A	N/A
15	IDC	95	95	0	Negative	1.9	1.1
16	IDC	95	95	0	Negative	2.0	0.25
17	IDC	95	80	0	Negative	1.9	1.1
18	IDC	70	95	3+	Positive	10.6	5.8
19	IDC	95	95	0	N/A	N/A	N/A
20	IDC	50	10	3+	Positive	N/A	N/A
21	IDC	40	60	3+	Positive	16.2	6.7
22	IDC	0	0	0	Negative	1.9	1.1
23	IDC	70	0	3+	Positive	14.7	7.7
24	IDC	90	95	1+	Positive	8.4	4.8
25	IDC	5	0	3+	Positive	12.1	6.7
26	IDC	N/A	N/A	N/A	N/A	N/A	N/A
27	IDC	95	40	0	Negative	4.1	1.3

N/A not available.

Table 3 Hormone receptors and HER2 results in ductal carcinoma in situ (DCIS) and invasive carcinoma.

	ER+/HER2+	ER+/HER2−	ER−/HER2+	ER−/HER2−	Total
DCIS	2	2	4	0	8
Invasive carcinoma	9	7	0	1	17
Total	11 (44%)	9 (36%)	4 (16%)	1 (4%)	25

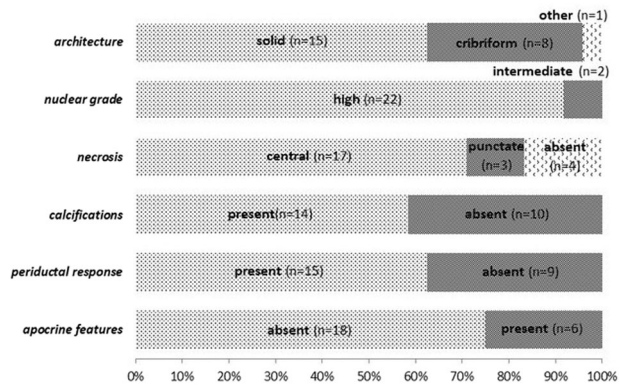

Fig. 3 Morphologic features of ductal carcinoma in situ (DCIS). The bar chart shows the distribution of histologic features of 9 DCIS cases.

overexpression of p53 protein in >50% of tumor cells (Table 4; Fig. 2b). Four cases with missense mutations showed p53 expression in 5–50% of tumor cells. All cases with nonsense, deletion, and splice-site mutations ($n = 10$) showed little to no expression (<1%, null pattern; Fig. 4b). The type of germline mutation did not correlate with ER or HER2 status (Table 5). In addition, no association was found between type of mutation and histomorphology (data not shown).

Discussion

In this report, we describe in detail the morphologic features of invasive and in situ carcinomas in LFS. In our cohort of 27

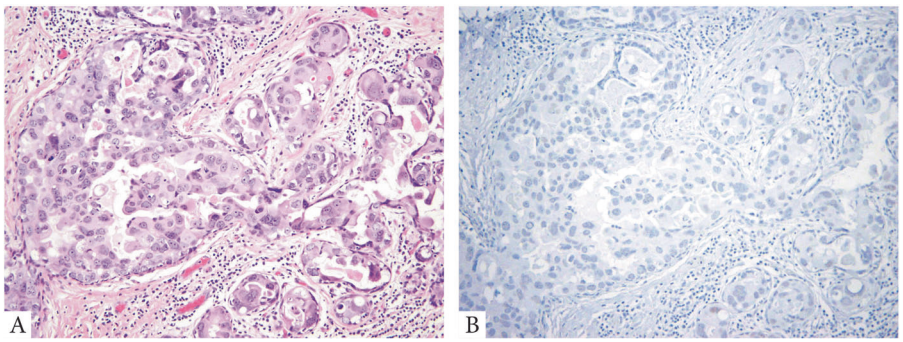

Fig. 4 Example of ductal carcinoma in situ (DCIS). Case 3: High-grade DCIS (**a**) in a patient with a germline TP53 deletion showing absent p53 expression (**b**; null pattern).

Table 4 P53 immunohistochemistry (IHC) in tumor tissue and correlation with germline mutation.

	P53 IHC in tumor cells		
	<1%	1–50%	>50%
Germline mutation			
Missense	0	4	9
Nonsense	6	0	0
Deletion	2	0	0
Splice	2	0	0
N/A	1	0	1
Total	11	4	10

N/A not available.

Table 5 Hormone receptors and HER2 results according to type of TP53 germline mutation.

	ER+/ HER2+	ER+/ HER2−	ER−/ HER2+	ER−/ HER2−	Total
Missense	5	7	1	1	14
Nonsense	3	2	2	0	7
Deletion	1	1	0	0	2
Splice	1	1	0	0	2
N/A	1	0	1	0	2
Total	11 (41%)	11 (41%)	4 (15%)	1 (4%)	27

N/A not available

cases from 25 patients with germline *TP53* mutations, both invasive and in situ carcinomas showed features similar to breast tumors with somatic *TP53* mutations and distinct from other germline-associated cancers [9, 17–20]. Invasive carcinomas in our cohort were most often mSBR high grade, similar to invasive breast cancer with somatic *TP53* mutations [21] and DCIS was most often high nuclear grade, solid type, with central necrosis, similar to DCIS with somatic *TP53* mutations [22, 23]. While both *BRCA1*- and *BRCA2*-associated tumors show high mSBR grade they also tend to have pushing borders [10, 18, 24] and *BRCA1*-associated tumors are also associated with dense lymphocytic infiltrate and syncytial growth pattern. Pushing borders, dense lymphocytic infiltrate, and syncytial growth pattern are features rarely seen in the LFS-associated breast cancers in our study.

Our findings are similar to those recently reported by Packwood et al. [25]. In their study, which included 36 cases of invasive carcinoma and 9 containing DCIS only they found that the majority of invasive carcinomas were IDC of no special type, high mSBR grade (50%, 18/36), and HER2+ (55%, 20/36). In addition, they found that cancers in TP53 carriers were more likely to be associated with a densely sclerotic stroma compared to noncarriers, and showed high levels of αvβ6 integrin, α-SMA and pSMAD2/3 expression on IHC, suggesting that the dense stromal phenotype may be driven by upregulated TGFβ signaling. The type of stroma was not a variable that we were able to accurately evaluate in our study cohort, and this interesting finding should be validated in further studies.

LFS-associated breast cancer has been shown to be enriched for HER2-positive disease (53–83%) and in about half of all cases is both ER-positive and HER2-positive [2, 7, 8]. In a prior report including all the cases from the current study, 84% of LFS invasive breast cancers were positive for ER and/or PR and 81% were high grade. Sixty-three percent of invasive and 73% of in situ carcinomas were positive for HER2 (IHC 3+ or FISH amplified). Of the invasive tumors, 53% were positive for both ER and HER2 and DCIS was positive for ER and HER2 in 27% of the cases. The percentage of HER2 positivity seen in the current study is slightly lower than that previously reported by the LFS Consortium (60% vs 66%) [2], likely reflecting the particular mix of cases with tissue available for additional studies. It is worth noting the rates of HER2 positivity in invasive carcinoma are much higher than reported for breast cancer overall (53% vs 15%) [26]. In addition, all these HER2+ LFS-associated invasive carcinomas were also ER +, which is the rarest breast cancer subtype (only seen in 10% of breast cancers in the general population) [26]. In this study, ER+/HER2+ invasive carcinomas showed lower ER expression compared to ER+/HER2 negative cancers (mean ER expression 58% vs 92%), similar to non-LFS tumors [27]. The morphology of LFS-associated breast cancers is not entirely unique and shares features with

unselected HER2+ disease, although with higher mSBR grade and less tendency to show apocrine features [28, 29].

Somatic *TP53* mutations are frequent drivers in sporadic breast cancer, with an overall rate of *TP53* mutation in breast cancer of about 28% [21] and higher rates in basal-like (65%) and HER2 enriched subtypes (53%) [21]. Prior studies have shown the distribution of *TP53* mutations in germline and sporadic tumors to be similar, with about 75% of all mutations being missense mutations, primarily in the DNA-binding domain (exons 5–8), and a much lower fraction of other mutation types, including nonsense, frameshift, deletion, and splice-site mutations [30, 31]. Strong overexpression of p53 protein was seen in the single case in our current study for which the actual mutation sequence is not available, supporting a probable missense mutation; thus, the overall mutation distribution in the current study is 56% missense (15/27) and 44% non-missense (12/27). The somewhat higher proportion of non-missense mutations in the current cohort relative to prior studies may reflect improved current detection strategies, particularly for the detection of non-missense mutations and mutations in areas outside the DNA-binding domain. In the current study, tumors with high p53 protein expression were more commonly seen in individuals with *TP53* germline missense mutations, whereas cases negative for p53 expression (or <1% nuclear expression) by IHC were seen in women carrying deletions or nonsense mutations. These patterns of immunoreactivity are similar to those previously reported for sporadic *TP53* mutated breast cancer [22, 32]. Several tumors in our study from patients with germline missense mutations were associated with only moderate expression of p53 protein (5–40%), which may reflect tumor-specific regulatory mechanisms [33].

The morphologic features of LFS-associated breast cancers are not pathognomonic and are similar to those tumors with somatic *TP53* mutations [21]. However, it is important to raise awareness among pathologists and clinicians of enrichment of ER+/HER2+ tumors in patients with germline *TP53* mutations. The prevalence of germline TP53 mutations in an unselected cohort of breast cancer patients under the age of 50 with HER2+ disease has been previously reported at 1.4% [34]. Based on the clinical importance of correctly identifying germline *TP53* carriers, consideration should be given to germline testing, with a panel including the TP53 gene, to young patients with HER2+ breast cancer, especially if there is a notable family history, regardless of morphology.

Limitations of our study include the retrospective nature, the limited number of slides available for pathology review, with only biopsy material available for some cases, and the age of stored paraffin blocks (some >40 years). LFS has been challenging to study, not only because the syndrome is rare and has high mortality, but also because of the complexity of the *TP53* gene and its many roles in tumorigenesis. At the current time, there is little published data on the molecular pathogenesis of breast cancer in LFS. Somatic *TP53* mutations have been reported in precursor lesions [22, 35], including atypical ductal hyperplasia [35, 36], and in DCIS [22]. These findings suggest that *TP53* inactivation occurs in preneoplastic lesions; however, the early steps in breast carcinogenesis in the setting of germline *TP53* mutations are poorly understood.

In conclusion, invasive carcinomas in LFS patients are most often high-grade but without the pushing borders, syncytial architecture and dense associated lymphocytic infiltrate characteristic of BRCA-associated cancers. More than half of *TP53* germline mutated cancers are HER2 positive, and many also show co-expression of ER. The type of germline mutation present does not appear to correlate with ER and HER2 status. Further studies linking specific *TP53* mutations or types of mutations with morphologic and molecular features may be helpful both for understanding disease pathogenesis and for the design of diagnostic and preventive strategies for LFS-affected individuals. In particular, studies of early lesions in LFS-associated breast cancer could be important for informing the design of trials of chemopreventive agents and potential environmental risk modifiers.

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Compliance with ethical standards

Conflict of interest DAD consults for Novartis and is on the Advisory Board for Oncology Analytics, Inc. JEG receives research support from Myriad Genetics, Ambry Genetics, Invitae Genetics, is leading two clinical trials for Astra-Zeneca, consults for Helix Genetics, is on the Scientific Advisory Board of Konica Minolta, and has received speaker's honorarium from Clinical Care Options, LLC. The other authors declare no conflict of interest.

References

1. WHO Classification of Tumours Editorial Board. Breast tumours. 5th ed. Lyon: IARC; 2019.
2. Masciari S, Dillon DA, Rath M, Robson M, Weitzel JN, Balmana J, et al. Breast cancer phenotype in women with TP53 germline mutations: a Li-Fraumeni syndrome consortium effort. Breast Cancer Res Treat. 2012;133:1125–30.
3. Verdial FC, Etzioni R, Duggan C, Anderson BO. Demographic changes in breast cancer incidence, stage at diagnosis and age associated with population-based mammographic screening. J Surg Oncol. 2017;115:517–22.
4. Kamihara J, Rana HQ, Garber JE. Germline TP53 mutations and the changing landscape of Li-Fraumeni syndrome. Hum Mutat. 2014;35:654–62.

5. AlHarbi M, Mubarak N, AlMubarak L, Aljelaify R, AlSaeed M, Almutairi A, et al. Rare TP53 variant associated with Li-Fraumeni syndrome exhibits variable penetrance in a Saudi family. NPJ Genom Med. 2018;3:35.
6. Mai PL, Best AF, Peters JA, DeCastro RM, Khincha PP, Loud JT, et al. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. Cancer. 2016;122:3673–81.
7. Wilson JRF, Bateman AC, Hanson H, An Q, Evans G, Rahman N, et al. A novel HER2-positive breast cancer phenotype arising from germline TP53 mutations. J Med Genet. 2010;47:771–4.
8. Melhem-Bertrandt A, Bojadzieva J, Ready KJ, Obeid E, Liu DD, Gutierrez-Barrera AM, et al. Early onset HER2-positive breast cancer is associated with germline TP53 mutations. Cancer. 2012;118:908–13.
9. Lakhani SR, Easton DF, Stratton MR, Breast Cancer Linkage Consortium. Pathology of familial breast cancer: differences between breast cancers in carriers of BRCA1 or BRCA2 mutations and sporadic cases. Lancet. 1997;349:1505–10.
10. Honrado E, Benitez J, Palacios J. The molecular pathology of hereditary breast cancer: genetic testing and therapeutic implications. Mod Pathol. 2005;18:1305–20.
11. Mai PL, Malkin D, Garber JE, Schiffman JD, Weitzel JN, Strong LC, et al. Li-Fraumeni syndrome: report of a clinical research workshop and creation of a research consortium. Cancer Genet. 2012;205:479–87.
12. Moore OS Jr, Foote FW Jr. The relatively favorable prognosis of medullary carcinoma of the breast. Cancer. 1949;2:635–42.
13. Ridolfi RL, Rosen PP, Port A, Kinne D, Miké V. Medullary carcinoma of the breast: a clinicopathologic study with 10 year follow-up. Cancer. 1977;40:1365–85.
14. Salgado R, Denkert C, Demaria S, Sirtaine N, Klauschen F, Pruneri G, et al. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. Ann Oncol. 2015;26:259–71.
15. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol. 2010;28:2784–95.
16. Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. Arch Pathol Lab Med. 2018;142:1364–82.
17. Schrader KA, Masciari S, Boyd N, Wiyrick S, Kaurah P, Senz J, et al. Hereditary diffuse gastric cancer: association with lobular breast cancer. Fam Cancer. 2008;7:73–82.
18. Bane AL, Beck JC, Bleiweiss I, Buys SS, Catalano E, Daly MB, et al. BRCA2 mutation-associated breast cancers exhibit a distinguishing phenotype based on morphology and molecular profiles from tissue microarrays. Am J Surg Pathol. 2007;31:121–8.
19. Banneau G, Guedj M, MacGrogan G, de Mascarel I, Velasco V, Schiappa R, et al. Molecular apocrine differentiation is a common feature of breast cancer in patients with germline PTEN mutations. Breast Cancer Res. 2010;12:R63.
20. Muranen TA, Blomqvist C, Dork T, Jakubowska A, Heikkilä P, Fagerholm R, et al. Patient survival and tumor characteristics associated with CHEK2:p.I157T—findings from the Breast Cancer Association Consortium. Breast Cancer Res. 2016;18:98.
21. Silwal-Pandit L, Vollan HK, Chin SF, Rueda OM, McKinney S, Osako T, et al. TP53 mutation spectrum in breast cancer is subtype specific and has distinct prognostic relevance. Clin Cancer Res. 2014;20:3569–80.
22. Done SJ, Arneson CR, Ozcelik H, Redson M, Andrulis IL. P53 protein accumulation in non-invasive lesions surrounding p53 mutation positive invasive breast cancers. Breast Cancer Res Treat. 2001;65:111–8.
23. O'Malley FP, Vnencak-Jones CL, Dupont WD, Parl F, Manning S, Page DL. p53 mutations are confined to the comedo type ductal carcinoma in situ of the breast. Immunohistochemical and sequencing data. Lab Investig. 1994;71:67–72.
24. Lakhani SR, Jacquemier J, Sloane JP, Gusterson BA, Anderson TJ, van de Vijver MJ, et al. Multifactorial analysis of differences between sporadic breast cancers and cancers involving BRCA1 and BRCA2 mutations. J Natl Cancer Inst. 1998;90:1138–45.
25. Packwood K, Martland G, Sommerlad M, Shaw E, Moutasim K, Thomas G, et al. Breast cancer in patients with germline TP53 pathogenic variants have typical tumour characteristics: the Cohort study of TP53 carrier early onset breast cancer (COPE study). J Pathol Clin Res. 2019;5:189–98.
26. Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LA, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst 2014;106:dju055.
27. Konecny G, Pauletti G, Pegram M, Untch M, Dandekar S, Aguilar Z, et al. Quantitative association between HER-2/neu and steroid hormone receptors in hormone receptor-positive primary breast cancer. J Natl Cancer Inst. 2003;95:142–53.
28. Lee HJ, Park IA, Park SY, Seo AN, Lim B, Chai Y, et al. Two histopathologically different diseases: hormone receptor-positive and hormone receptor-negative tumors in HER2-positive breast cancer. Breast Cancer Res Treat. 2014;145:615–23.
29. Bhargava R, Beriwal S, Striebel JM, Dabbs DJ. Breast cancer molecular class ERBB2: preponderance of tumors with apocrine differentiation and expression of basal phenotype markers CK5, CK5/6, and EGFR. Appl Immunohistochem Mol Morphol. 2010;18:113–8.
30. Kleihues P, Schauble B, zur Hausen A, Esteve J, Ohgaki H. Tumors associated with p53 germline mutations: a synopsis of 91 families. Am J Pathol. 1997;150:1–13.
31. Olivier M, Goldgar DE, Sodha N, Ohgaki H, Kleihues P, Hainaut P, et al. Li-Fraumeni and related syndromes: correlation between tumor type, family structure, and TP53 genotype. Cancer Res. 2003;63:6643–50.
32. Alsner J, Jensen V, Kyndi M, Offersen BV, Vu P, Borresen-Dale AL, et al. A comparison between p53 accumulation determined by immunohistochemistry and TP53 mutations as prognostic variables in tumours from breast cancer patients. Acta Oncol. 2008;47:600–7.
33. Goh AM, Coffill CR, Lane DP. The role of mutant p53 in human cancer. J Pathol. 2011;223:116–26.
34. Rath MG, Masciari S, Gelman R, Miron A, Miron P, Foley K, et al. Prevalence of germline TP53 mutations in HER2+ breast cancer patients. Breast Cancer Res Treat. 2013;139:193–8.
35. Mao X, Fan C, Wei J, Yao F, Jin F. Genetic mutations and expression of p53 in non-invasive breast lesions. Mol Med Rep. 2010;3:929–34.
36. Keohavong P, Gao WM, Mady HH, Kanbour-Shakir A, Melhem MF. Analysis of p53 mutations in cells taken from paraffin-embedded tissue sections of ductal carcinoma in situ and atypical ductal hyperplasia of the breast. Cancer Lett. 2004;212:121–30.