Cancer Treatment Reviews 114 (2023) 102522

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Tumour Review

Germline *TP53* pathogenic variants and breast cancer: A narrative review

Eva Blondeaux [a,*], Luca Arecco [b,c], Kevin Punie [d], Rossella Graffeo [e], Angela Toss [f], Carmine De Angelis [g], Lucia Trevisan [h], Giulia Buzzatti [h], Sabine C. Linn [i], Peter Dubsky [j], Mara Cruellas [k], Ann H. Partridge [l], Judith Balmaña [k], Shani Paluch-Shimon [m], Matteo Lambertini [b,c]

[a] Clinical Epidemiology Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[b] Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genova, Genoa, Italy
[c] Department of Medical Oncology, U.O. Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[d] Department of General Medical Oncology, University Hospitals Leuven, KU Leuven, Leuven, Belgium
[e] Oncology Institute of Southern Switzerland, EOC, Bellinzona, Switzerland
[f] Department of Oncology and Hematology, University Hospital of Modena, Modena, Italy
[g] Department of Clinical Medicine and Surgery, University Federico II, Naples, Italy
[h] Hereditary Cancer Unit, Oncologia Medica 2, IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[i] Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands
[j] Breast Centre, Hirslanden Klinik St Anna, Luzern, Switzerland
[k] Department of Medical Oncology, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain
[l] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA
[m] Breast Cancer Unit, Sharett Institute of Oncology, Hadassah Medical Center & Faculty of Medicine, Hebrew University, 91120 Jerusalem, Israel

ARTICLE INFO

Keywords:
Breast cancer
TP53
Prognosis
Treatment

ABSTRACT

Approximately 10% of breast cancers are associated with the inheritance of a pathogenic variant (PV) in one of the breast cancer susceptibility genes. Multiple breast cancer predisposing genes, including *TP53*, are responsible for the increased breast cancer risk.

Tumor protein-53 (*TP53*) germline PVs are associated with Li-Fraumeni syndrome, a rare autosomal dominant inherited cancer predisposition syndrome associated with early-onset pediatric and multiple primary cancers such as soft tissue and bone sarcomas, breast cancer, brain tumors, adrenocortical carcinomas and leukemias. Women harboring a *TP53* PV carry a lifetime risk of developing breast cancer of 80–90%.

The aim of the present narrative review is to provide a comprehensive overview of the criteria for offering *TP53* testing, prevalence of *TP53* carriers among patients with breast cancer, and what is known about its prognostic and therapeutic implications. A summary of the current indications of secondary cancer surveillance and survivorship issues are also provided. Finally, the spectrum of *TP53* alteration and testing is discussed.

The optimal strategies for the treatment of breast cancer in patients harboring *TP53* PVs poses certain challenges. Current guidelines favor the option of performing mastectomy rather than lumpectomy to avoid adjuvant radiotherapy and subsequent risk of radiation-induced second primary malignancies, with careful consideration of radiation when indicated post-mastectomy. Some studies suggest that patients with breast cancer and germline *TP53* PV might have worse survival outcomes compared to patients with breast cancer and wild type germline *TP53* status. Annual breast magnetic resonance imaging (MRI) and whole-body MRI are recommended as secondary prevention.

Introduction

Breast cancer is the most common cancer diagnosis in women and the majority are considered sporadic cases [1]. Around 10% of breast malignancies are associated with a germline pathogenic variant in one of the breast cancer susceptibility genes and family history is often the telltale of an underlying inherited predisposition [2,3]. *BRCA1* and *BRCA2* pathogenic variants are responsible for less than half of the

* Corresponding author at: IRCCS Ospedale Policlinico San Martino, Clinical Epidemiology Unit, Largo Rosanna Benzi 10, 16132 Genova, Italy.
E-mail address: evablondeaux@gmail.com (E. Blondeaux).

https://doi.org/10.1016/j.ctrv.2023.102522
Received 5 December 2022; Received in revised form 24 January 2023; Accepted 26 January 2023
Available online 31 January 2023

variants involved in increased breast cancer risk and pathogenic variants in multiple other breast cancer predisposing genes, including *TP53*, are responsible for the remaining [4–6].

Tumor protein-53 (*TP53*) gene is a tumor suppressor which controls cell growth and division. It protects cells against genome changes resulting from DNA damage by suppressing proliferation or activating apoptosis [7]. *TP53* germline pathogenic variants are associated with heritable *TP53*-related cancer syndromes, classically named Li-Fraumeni syndrome (https://www.omim.org/entry/151623), a rare autosomal dominant inherited cancer predisposition syndrome historically associated with early-onset pediatric and multiple primary cancers such as soft tissue and bone sarcomas, breast cancer, brain tumors, adrenocortical carcinomas, gastrointestinal, lung, pancreatic and prostate cancers and leukemias [8–12]. More recently *TP53* pathogenic variants were associated also with an increased risk of prostate cancer [13]. The cumulative cancer risk associated with Li-Fraumeni syndrome has been estimated to be approximately 50% by the age of 40 years and up to 90% by the age of 60 years [14] with females reported to have a higher risk than males, mostly due to the increased risk of premenopausal breast cancer [15–17]. Indeed, healthy women harboring a *TP53* pathogenic variant carry a lifetime risks of developing breast cancer of around 80–90%, higher than the risk of healthy *BRCA* carriers (lifetime risk of around 60–85%) [18–21].

The aim of the present narrative review is to give a comprehensive overview of all the aspects to be considered during the counselling of women with a new diagnosis of breast cancer and carrying (or suspected to carry) a *TP53* pathogenic variant. Criteria for offering *TP53* testing, prevalence of *TP53* carriers among patients with breast cancer, prognostic and therapeutic implications are provided. Current indications of secondary cancer surveillance and survivorship issues are discussed. Finally, the spectrum of *TP53* alteration and testing is discussed.

Criteria for offering *TP53* testing and prevalence of *TP53* carriers among patients with breast cancer

Different criteria for offering *TP53* testing have been proposed (Table 1).

The first Li-Fraumeni syndrome criteria were proposed by Li and Fraumeni in 1988 [22]. Subsequently, less stringent Li-Fraumeni-like criteria were proposed in order to expand the proband's cancer types to include childhood cancers, brain cancers, and adrenal cortical carcinoma, and to change the relatives' age at the time of diagnosis to < 60 years [23,24]. Broader criteria were proposed by Chompret and colleagues in 2001 and a modified version of the Chompret criteria was proposed by Bougeard and colleagues in 2015 with the recommendation to offer *TP53* testing to patients with breast cancer diagnosis before age 31, regardless of family history [25,26]. Sensitivity and specificity of these criteria have been estimated to be around 90% and 50% respectively [26,29–31]. However, *TP53* carriers could also be identified in families who do not fulfill these clinical criteria due to a wide variety of phenotypes within the same syndrome, different tumor spectrum, age at diagnosis or sporadic occurrence of a germline pathogenic variant [26,30]. Indeed, it is estimated that at least 14% of germline *TP53* carriers have a *de novo* pathogenic variant [32]. Thus, the lack of a positive family history does not exclude the possibility of the identification of a *TP53* pathogenic variant in the patient [33].

In 2020, the European Reference Network GENTURIS expanded the revised Chompret criteria. Children and adolescents with acute lymphoblastic leukemia, medulloblastoma or jaw osteosarcoma, as well as children with any type of cancer from southern and south-eastern Brazilian families and patients affected by second primary malignancy within the radiotherapy field of a first core *TP53* tumor were also considered eligible for *TP53* testing [27]. Despite the available evidence regarding the higher prevalence of human epidermal growth factor receptor 2 (HER2) positive breast cancer among *TP53* carriers [34], none of the above-mentioned criteria consider histopathological features of

Table 1
Criteria for offering *TP53* testing.

Criteria	Year	General criteria
Classic Li–Fraumeni criteria [22]	1988	Proband with sarcoma diagnosed before 45 years *AND* First-degree relative with any cancer before 45 years *AND* First or second-degree relative with any cancer before 45 years or a sarcoma at any age
Birch criteria (LFL) [23]	1994	Proband with any childhood cancer, or a sarcoma, or a brain tumor or ACC before 45 years *AND* First or second-degree relative with a core LFS cancer (sarcoma, breast cancer, brain tumor, ACC or leukemia) at any age *AND* First or second-degree relative with any cancer before 60 years
Eeles criteria (LFL) [24]	1995	Two first- or second-degree relatives with core LFS malignancies (sarcoma, premenopausal breast cancer, brain tumor ACC, leukemia, lung [bronchoalveolar] cancer) at any age
Chompret criteria [25]	2001	Proband affected by a narrow spectrum cancer (i.e., sarcomas, brain tumors, breast cancer, and ACC) before 36 years *and* at least one first or second-degree relative affected by a narrow spectrum tumor (other than breast cancer if the proband is affected by breast cancer) before 46 years or multiple primary tumors *OR* Proband with multiple primary tumors; two of which belong to the narrow spectrum with the first of which occurred before 36 years *OR* Proband with ACC
Modified Chompret criteria [26]	2015	Proband with tumor belonging to LFS tumor spectrum (e.g., soft tissue sarcoma, osteosarcoma, brain tumor, breast cancer, ACC, leukemia, bronchoalveolar lung cancer) before 46 years *and* at least one first- or second-degree relative with an above LFS tumor (except breast cancer if proband has breast cancer) before 56 years or with multiple tumors at any age *OR* Proband with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum and the first occurring before 46 years *OR* Patient with ACC, choroid plexus carcinoma, or rhabdomyosarcoma of embryonal anaplastic subtype, irrespective of family history *OR* Breast cancer before age 31 years
GENTURIS criteria* [27]	2020	Patient with a *TP53* core tumor (breast cancer, soft-tissue sarcoma, osteosarcoma, central nervous system tumor, ACC) before 46 years *and* at least one first- or second-degree relative with a core tumor before 56 years *OR* Patient with multiple tumors, including two *TP53* core tumors, the first of which occurred before 46 years, irrespective of family history *OR* Patient with ACC, choroid plexus carcinoma, or rhabdomyosarcoma of embryonal anaplastic subtype, irrespective of family history *OR* Breast cancer before age 31 years *OR* Children and adolescents with hypodiploid ALL or otherwise unexplained sonic hedgehog-driven medulloblastoma or jaw osteosarcoma *OR* Patients who develop a second primary tumor, within the radiotherapy field of a first core *TP53* tumor which occurred before 46 years

(*continued on next page*)

Table 1 (*continued*)

Criteria	Year	General criteria
		OR Children with any cancer from southern and south-eastern Brazilian families [a]
Evans criteria* [28]	2020	Invasive breast carcinoma or DCIS before 31 years *OR* Bilateral invasive breast carcinoma or DCIS *or* multifocal invasive breast carcinoma *or* HER2 + invasive breast carcinoma *or* phyllode tumor before 36 years *OR* Invasive breast carcinoma *and* a second *TP53* core tumor in the patient before 46 years *OR* Invasive breast carcinoma before 46 years *and* one first- or second-degree relative with a *TP53* core tumor before 56 years

Abbreviations: ACC, adrenocortical carcinoma; LFS, Li–Fraumeni syndrome; LFL, Li–Fraumeni-like; ALL, acute lymphoblastic leukemia; DCIS, ductal carcinoma in situ; HER2, human epidermal growth factor receptor 2.

* Breast cancer-specific testing criteria, not formally tested for sensitivity and specificity.

[a] To be tested for the p.R337H Brazilian founder germline *TP53* variant.

breast cancer. In breast cancer-specific testing criteria proposed by Evans and colleagues, different age thresholds are proposed for patients with HER2 positive breast cancer or phyllode tumor [28].

Recommendations about *TP53* testing derive from several studies evaluating the prevalence of *TP53* germline carriers in selected patients with breast cancer (Table 2).

In highly selected cohorts of patients around 5% harbor a *TP53* germline pathogenic variant, including women with breast cancer who meet the criteria of heritable *TP53*-related cancer syndromes or even those who have a strong family history of breast cancer [26,30,36,37,41,42,51–53]. Whereas the frequency of *TP53* germline carriers in unselected patients with breast cancer is less then 0.5% [5,6,54]. In two population-based study that aimed to estimate the cancer risk related to different breast cancer susceptibility genes, *TP53* pathogenic variant were identified in 19 (0.06%) out of 32,247 unselected patients with breast cancer (CARRIERS consortium) and in 7 (0.01%) out of 48,826 unselected patients with breast cancer (Breast Cancer Association Consortium) [5,6].

In a cohort of 364 female patients from the Netherlands diagnosed with breast cancer before the age of 30 years, 8 (2.2%) patients harbored a (likely) pathogenic *TP53* variant [33]. Among them, 6 patients had a personal or familial history suggestive of Li-Fraumeni syndrome [33]. In an Australian population-based cohort of invasive breast cancers, *TP53* (likely) pathogenic variants were detected in 2 (4%) out of 52 women diagnosed before age of 30 unselected for family history and in 3 (7%) out of 42 women diagnosed in their 30s with two or more first- or second-degree relatives with breast or ovarian cancer [40]. In a cohort of 100 Polish females with breast cancer diagnosed before the age of 30 years and positive family history of cancer, prevalence of *TP53* pathogenic variant was 4% [48].

To note that the identification of a pathogenic variant can be influenced by the method used to detect the variant, thus absolute frequencies of *TP53* germline carriers should be interpreted with caution.

The introduction of next-generation sequencing technique, the broader diagnostic criteria and more inclusive testing criteria will lead to a considerably higher prevalence of germline *TP53* pathogenic variants detection and the identification of less penetrant Li-Fraumeni

Table 2
Studies exploring *TP53* germline pathogenic variant prevalence among selected patients with breast cancer.

Author	Year	Selection criteria	No. of pts tested	*BRCA1/2* status	*TP53* (likely) pathogenic variant prevalence (%)
Evans DGR et al [35]	2002	Probands with sarcoma and BC (BC in proband or in a first degree relative) in family not fulfilling LFS	21	Negative	4.8% (1/21)
Walsh T et al [36]	2006	Probands from families with 4 or more cases of BC or ovarian cancer	300	12% *BRCA1/2* mutated	1% (3/300)
Lalloo F et al [37]	2006	BC ≤ 30 years	100	18% *BRCA1/2* mutated	4% (4/100)
Manoukian S et al [38]	2007	Unrelated individuals from families with one case of sarcoma and at least one case of BC	23	Negative	13% (3/23)
Ginsburg OM et al [39]	2009	BC < 30 years	95	Negative	0% (0/95)
Gonzalez KD et al [30]	2009	BC between 30 and 49 years	14	Negative	7.1% (1/14)
Mouchawar Jet al [40]	2010	(a) women diagnosed with BC before the age of 30 years irrespective of family history	(a) 52	Negative	(a) 4% (2/52)
		(b) women diagnosed with BC between 30 and 39 years with two or more first- or second-degree relatives with BC or ovarian cancer	(b) 42	Negative	(b) 7% (3/42)
Lee DSC et al [41]	2012	BC < 37 years	83	Negative	4.8% (4/83)
McCuaig JM et al [42]	2012	BC < 30 years	28	Negative	21.4% (6/28)
Rath MG et al [43]	2013	HER2-positive BC, <51 years	213	Negative	1.4% (3/213)
Carraro DM et al [44]	2013	BC < 35 years	43	Negative	2.3% (1/43)
Bougeard G et al [26]	2015	BC < 31 years	NR	NR	6% (NR)
Eccles DM et al [45]	2016	HER2-positve BC, <31 years	71	Negative	8.5% (5/71)
Hahn EC et al [46]	2018	Women with BC diagnosed before 46 years and without Chompret criteria for LFS or LFL	239	Negative	2.5% (6/239)
Bakhuizen JJ et al [33]	2019	BC < 30 years	364	19/364 *BRCA1/2* mutated	2.2% (8/364)
Gallardo-Alvarado LN et al [47]	2019	BC < 45 years	78	Negative	6.4% (5/78)
Rogoża-Janiszewska E et al [48]	2020	BC ≤ 30 years	100	Negative	4% (4/100)
Siraj AK et al [49]	2021	BC ≤ 40 years	464	57/464 *BRCA1/2* mutated	1.5% (7/464)
Waks AG et al [50]	2022	BC ≤ 35 years	92	13/92 *BRCA1/2* mutated	1.1% (1/92)

Abbreviations: BC, breast cancer; FH, familial history; LFS, Li-Fraumeni syndrome; LFL, Li-Fraumeni-Like syndrome; NR, not reported.

syndrome [19,37]. In fact, multigene panel studies gave the possibility to broaden the phenotypic spectrum of Li-Fraumeni syndrome identifying *TP53* germline pathogenic variants in individuals who do not fulfill established clinical criteria for Li-Fraumeni syndrome testing [12,54,55].

Breast cancer subtypes arising in *TP53* carriers

Patients harboring *TP53* pathogenic variants may develop distinct breast cancer subtypes. Some previous reports suggested that patients harboring germline *TP53* pathogenic variants are more likely to develop HER2-positive breast cancers (Table 3).

In particular, a multicenter international case-control analysis of the BRIDGES study including 42,680 patients and 46,387 controls aimed to characterize tumors associated with different breast cancer susceptibility genes [34]. Among the 42,680 patients included, 51 harbored a *TP53* pathogenic variant. *TP53* carriers were found to have a greater chance to develop HER2-positive breast cancers (46% of cases) [34]. Moreover, *TP53* carriers were more likely to have mixed lobular and ductal tumors than ductal carcinoma (OR 7.01, 95% CI 3.04–16.17) [34]. In a Brazilian cohort of 91 *TP53* female carriers, breast cancer was the first malignancy diagnosed in 90% of the women, of whom 78% had an early-onset breast cancer (i.e. age ≤ 45 years) [64]. Moreover, bilateral breast cancer was observed in 29% of the patients. Overall, 41% of the tumors were HER2-positive, and 33% were positive for both hormone receptor and HER2 [64].

Many other studies with<50 patients provided similar results with a prevalence of HER2 positivity ranging between 34 and 83% (Table 3) [33,56–63], clearly higher than expected in an unselected breast cancer population (15–20%) [65,66].

Breast cancer prognosis

Several studies evaluated survival outcomes of patients with breast cancer according to somatic *TP53* pathogenic variants [67–70]. However, few data are available regarding clinical outcomes of patients with breast cancer according to germline *TP53* mutation status. In a cohort of 10,053 unselected Chinese patients with early-stage breast cancer, the 50 patients with a germline *TP53* pathogenic variant had significantly worse relapse-free survival (adjusted HR = 2.24; 95%CI 1.15–4.33; p = 0.02), distant relapse-free survival (adjusted HR = 2.73; 95%CI 1.41–5.30; p = 0.003) and overall survival (adjusted HR = 4.60; 95%CI, 2.26–9.41; p < 0.001) as compared to patients with early stage breast cancer and wild type *TP53* germline status [8]. A second study, including the first cohort of 10,053 unselected Chinese patients with breast cancer and a second cohort of 1820 patients with breast cancer selected by age at diagnosis or family history of any cancer, demonstrated that the rate of ipsilateral breast tumor recurrence after breast conserving surgery was significantly higher in *TP53* carriers than in non-carriers (21.1% vs 3.8%) [71]. Moreover, the 10-year risk of contralateral breast cancer in *TP53* carriers was significantly higher than that in non-carriers (17.9% vs 3.6%; HR 7.0 95% CI 3.3–14.9; p < 0.001) [71].

A study conducted by Hyder and colleagues in England aimed to determine the risk of contralateral breast cancer in *BRCA1* (N = 218), *BRCA2* (N = 132), and *TP53* (N = 47) carriers with very early-onset (<36 years) breast cancer [72]. Results indicate that the risk of contralateral breast cancer was significantly higher in *TP53* carriers compared to *BRCA1* and *BRCA2* carriers. The 10 and 20-year cumulative risk of contralateral breast cancer was 53% (95%CI 30–81) and 82% (95%CI 50–99) for *TP53* carriers as compared to 32% (95% CI 24–43) and 57% (95% CI 45–69) in *BRCA1* carriers and 21% (95% CI 13.0–32.1) and 45% (95% CI 31.4–61.9) for *BRCA2* carriers [72]. The difference in 10-year cumulative risk of contralateral breast cancer in *TP53* carriers among these two studies (i.e., 17.9% in the Chinese and 53% in the English study) could be attributable to the different populations, being unselected for the first one and highly selected for the second one.

To our knowledge, no data are available regarding survival outcomes of metastatic breast cancer patients according to germline *TP53* mutational status.

Table 3
Tumor subtypes among *TP53* carriers.

Author	Year	*TP53* carriers with BC N	HER2 positive tumors N	Other findings
Wilson JRF et al [56]	2010	12*	10* (83%)	–
Melhem-Bertrandt A et al [57]	2012	30	20 (67%)	–
Masciari S et al [58]	2012	32*	20 (63%)	–
Bakhuizen JJ et al [33]	2019	8	5 (63%)	–
Packwood K et al [59]	2019	36	20 (56%)	–
Le A et al [60]	2020	38*	22 (58%)	–
Alyami H et al [61]	2021	21*	10 (53%)	2 cases of malignant phyllodes tumor
Kuba MG et al [62]	2021	17	9 (53%)	2 cases of HER2 negative BC by IHC (1 +) but positive by FISH.
Rippinger N et al [63]	2021	32	11 (34%)	10 cases (31.3%) of luminal B-like BC
Breast Cancer Association Consortium, Mavaddat N et al [34]	2022	51	NR (46%)	OR for HER2 + BC 7.14 (95%CI 3.34–15.28)
Sandoval RL et al [64]	2022	87	32 (41%)	43 cases (55%) of luminal-like BC

Abbreviations: HER2, human epidermal growth factor receptor 2; OR, odds ratio; IHC, immunohistochemistry; FISH, Fluorescence In Situ Hybridization; BC, breast cancer.
* invasive breast cancers.

Anticancer treatments

Special considerations regarding breast cancer treatment in *TP53* carriers are required.

As suggested by different studies, the risk of secondary radiation-induced malignancies reaches up to more than 30% among patients with *TP53* pathogenic variants treated with adjuvant radiotherapy. Among 16 Brazilian patients with breast cancer and germline *TP53* p. R337H pathogenic variant, 12 received adjuvant radiotherapy. After a median follow-up exceeding 50 months, 2 (16.7%) patients developed a radiotherapy-induced sarcoma [73]. In a group of 18 patients with a *TP53* pathogenic variant treated with radiation in a curative setting, after a median follow-up of 12.5 years, 2 (11.1%) patients developed a radiation-induced malignancy: one patient developed thyroid cancer, and the other developed sarcoma in the radiation field [60]. In a French cohort of 8 Li–Fraumeni patients with breast cancer, 6 received radiotherapy and 2 of them (33.3%) developed a secondary malignancy in the radiation field after a median follow-up of 6 years [74]. The secondary malignancies documented were an angiosarcoma and a fibrosarcoma [74]. Moreover, one patient developed papillary thyroid carcinoma inside the radiation field [74]. Other smaller case-series showed similar results [61,75–77].

Due to the risk of radiation-induced secondary malignancies after radiotherapy, a careful decision-making process with regard to risk–benefit ratios on the use of radiotherapy in patients with breast cancer harboring a germline *TP53* pathogenic variant is warranted. Current guidelines recommend that decisions about adjuvant radiotherapy should be considered with a multidisciplinary team and patient, with careful weighing of the risks and benefits, especially for patients

who need adjuvant radiotherapy after mastectomy [78].

To our knowledge, no evidence is available on the safety of radiation-guided imaging, such as bone scintigraphy, computed tomography scans and positron emission tomography scans, in patients with *TP53* pathogenic variant.

Regarding surgical management, several considerations should be made. Current guidelines recommend that radiation therapy should be avoided whenever possible due to the risk of radiation-induced secondary malignancies and that mastectomy rather than lumpectomy is preferable [27,78–80]. Moreover, as observed in *BRCA* carriers who have a significantly increased risk of further loco-regional disease but no increased risk of dying when treated with breast conserving surgery as compared to mastectomy, we might assume that similarly, mastectomy could also play a role in reducing the role of locoregional recurrences in *TP53* carriers [81]. However, no robust data are available in this population.

No information on the prognostic impact of the timing of risk-reducing mastectomy on life expectancy is available among *TP53* carriers. A study performed in *BRCA* carriers seem to indicate that the benefit of risk-reducing mastectomy is higher if mastectomy is performed at the age of 25 years but the benefit declines rapidly with increasing age at surgery [82]. Thus, due to the higher risk of contralateral breast cancer in *TP53* carriers compared to *BRCA1* and *BRCA2* carriers, current guidelines recommend discussing contralateral risk-reducing mastectomy [78]. However, the other cancer risks associated with *TP53* pathogenic variants should be taken into account during the surgical counselling [72].

Regarding the use of chemotherapy, Kasper and colleagues suggested that radiotherapy and genotoxic chemotherapies could increase the risk of new tumor development in a Li-Fraumeni syndrome mouse model. In particular, *TP53* mutant mice exposed to genotoxic agent (i.e. etoposide) had an increased risk of tumor development, whereas the exposure to non-genotoxic mitotic spindle agents (i.e. docetaxel) had no impact [83]. In humans, the demonstration of the potential contribution of chemotherapy to the development of subsequent primary tumors among *TP53* carriers derives from patients treated for childhood cancers [84]. Based on these findings, the European Reference Network GENTURIS recommends that priority should be given to surgical or ablative treatments, avoiding radiotherapy and preferring the use of non-genotoxic chemotherapies in the treatment of *TP53*-associated neoplasms [27]. Focusing on breast cancer treatment, despite HER2-positive tumors is the most frequent subtype among patients with *TP53* pathogenic variants, no data on treatment response to different chemotherapeutic and targeted therapy agents are available. A small study showed that *TP53* carriers treated with carboplatin-containing neoadjuvant chemotherapy reached a higher rate of pathological complete response as compared to patients treated with standard anthracycline-based or taxane-based chemotherapy regimens [8]. Recently, poly ADP ribose polymerase inhibitors (PARPi) have been studied in patients with a pathogenic variant in homologous recombination genes other than *BRCA*. However, *TP53* is not involved in the homologous recombination path, thus germline *TP53* carriers were excluded from both the TBCRC-048 and the Talazoparib Beyond *BRCA* trial [85,86].

Survivorship

Guidelines recommend that *TP53* carriers should follow a dedicated cancer surveillance protocol [27,87,88]. Guidelines and recommendations for second primary cancer surveillance among adult female *TP53* carriers are summarized in Table 4.

Current guidelines agree to recommend annual breast magnetic resonance imaging (MRI) (from age 20) for breast cancer surveillance, and to discuss with patients the possibility to undergo risk-reducing mastectomy [27,78,80,89–91,88,87,92]. On the contrary, there is no consensus on the use of mammography, only routinely recommended by the NCCN guidelines and by the TORONTO protocol, [80,89] or in case

Table 4
Guidelines and recommendations for surveillance in adult female *TP53* carriers.

	Breast cancer surveillance	Other cancers surveillance
TORONTO PROTOCOL [89]	- Clinical breast examination, every 6 months from age 20–25 or 5–10 years before the earliest case of breast cancer in the family. - Annual mammography and breast MRI from age 20 to 75 or 5–10 years before the earliest case of breast cancer in the family- Breast US with mammography (as indicated by breast density) - Consider RRM	- Complete clinical examination (including neurologic exam) and blood test every 3–4 months **Brain tumor** - Annual brain MRI **Soft tissue and bone sarcoma** - Annual WBMRI **GI tumors** - Colonoscopy every 2 years from age 25 or 10 years before the earliest known colorectal cancer in the family **Melanoma** - Annual dermatological examination
Modified TORONTO protocol - American guidelines [90]	- Clinical breast examination every 6 months from age 20 - Annual breast MRI from age 20 to 75 - Consider RRM	- Complete clinical examination every 6 months **Brain tumor** - Annual brain MRI (only first MRI with gadolinium enhancement) **Soft tissue and bone sarcoma** - Annual WBMRI Alternated to: - Annual US of abdomen and pelvis **GI tumors** - Upper endoscopy and colonoscopy every 2–5 years from age 25 **Melanoma** - Annual dermatological examination
ESMO guidelines [78]	- Clinical breast examination every 6–12 months from age 20–25 - Annual breast MRI from age 20 to 75. If MRI is not available, mammography may be considered. - Consider RRM	- Consider 6-monthly complete blood count **Brain tumor and sarcoma** - Consider annual WBMRI - Annual neurological examination **GI tumors** - Colonoscopy every 5 years from the age of 25 or as clinically indicated **Melanoma** - Annual dermatological examination
ESO-ESMO (BCY5) guidelines [91]	- Annual breast MRI and mammography with or without ultrasound	- Annual brain MRI - Annual WBMRI (without Gadolinium enhancement)
NCCN guidelines [80]	- Clinical breast examination, every 6–12 months from age 20 - Annual breast MRI from age 20 to 75 - Mammography considering tomosynthesis from age 30 - Consider RRM	- Clinical exam including neurologic examination every 6–12 months **Brain Tumor** - Annual brain MRI **Sarcoma** - Annual WBMRI **GI tumors** - Colonoscopy and upper endoscopy every 2–5 years from age 25 or 5 years before the earliest known colon or gastric cancer in the family

(*continued on next page*)

Table 4 (*continued*)

	Breast cancer surveillance	Other cancers surveillance
		Melanoma - Annual dermatological examination from the age of 18
The European Reference Network GENTURIS guidelines [27]	- Annual breast MRI from age 20 to 65 - Consider RRM	- Annual clinical examination **Brain Tumor** - Annual brain MRI until 50 years alternated to WBMRI (only the first with gadolinium enhancement) **Sarcoma** - Annual WBMRI (without gadolinium enhancement) **GI tumors** - Colonoscopy every 5 years from age 18 (Only if the carrier received abdominal radiotherapy for a previous cancer or if there is a family history of colorectal tumors suggestive of an increased genetic risk)
UKCGG Consensus Group guidelines [88]	- Annual breast MRI from age 20–70	- Routine clinical examination not recommended **Brain tumor** - Annual brain MRI (only first MRI with gadolinium enhancement) **Soft tissue and bone sarcoma** - Annual WBMRI (without gadolinium enhancement) **GI tumors** - Colonoscopy only indicated when family history of colorectal cancer or polyposis is present - Gastric endoscopy not indicated **Melanoma** - Annual dermatology review
Kumamoto et al 2021 [87]	- Breast exam twice a year from the age of 20 - Breast MRI every year from 20 to 75 years - Consider RRM	- Clinical examination every 6 months **Brain tumor** - Annual brain MRI (only first with gadolinium enhancement) **Soft tissue and bone sarcoma** - Annual WBMRI alternated to: - Annual US of abdomen and pelvis **GI tumors** - Upper endoscopy and colonoscopy every 2–5 years from age of 25 **Melanoma** - Annual dermatological examination
Australian Recommendations [92]	- Clinical breast examination every 6 months from age 20 - Annual breast MRI from age 20 - Consider RRM	**Brain tumor** - Annual brain MRI (only first with gadolinium enhancement) **Soft tissue and bone sarcoma** - Annual WBMRI (only first with gadolinium enhancement) **GI tumors** - Upper endoscopy and colonoscopy every 2–5 years from age 20–25 or younger dependent on family history **Melanoma** - Annual dermatological examination from age 18

Abbreviations: MRI, magnetic resonance imaging; US, ultrasound; RRM, risk reducing mastectomy; WBMRI, whole-body magnetic resonance imaging; GI, gastrointestinal.

the MRI could not be performed also taking into consideration that microcalcification are not optimally detected by MRI.

Considering the high risk of developing other tumors correlated with the presence of a germline *TP53* pathogenic variant, especially brain malignancies, soft tissue and bone sarcoma, melanoma, and the increased rate of gastrointestinal cancer, all guidelines agree to recommend annual whole-body MRI (generally from the age of 20) and annual brain MRI. Overall, there is agreement among guidelines that MRI should be preferred for secondary prevention over radiation-guided imaging. Conversely, there is no consensus whether or not to offer endoscopy surveillance of the upper and lower gastrointestinal tract: most guidelines suggest to tailor the indication and timing according to the family history. Many trials are currently ongoing with the aim of determine diagnostic efficacy of different surveillance imaging techniques and protocols among patients with *TP53* pathogenic variants (NCT03176836, NCT01464086, NCT02950987).

In summary, according to guidelines, surveillance for breast cancer should be based on annual breast MRI starting at the age of 20 and risk-reducing surgery should be discussed with the patients (Fig. 1). For brain tumors and sarcoma, annual whole-body MRI should be performed since birth while gastrointestinal and melanoma secondary prevention should be considered in adulthood (Fig. 2).

Regular follow up of patients with breast cancer should be scheduled based on current guidelines, considering not only the type of tumor, its biology and the treatment received, but also minimizing the diagnostic radiation in order to reduce the risk of radiation-induced secondary malignancies in these patients. Contrast-free diffusion-weighted whole-body MRI has proved to be effective for staging and follow-up in patients with breast cancer [89,93–96].

Finally, although limited evidence exist on the topic, all *TP53* carriers should be made aware of their risk of malignancy and the possible symptoms as well as encouraged to make positive lifestyle choices (e.g., not smoking, limit alcohol and red meat consumption, high fruits and vegetables intake, physical exercise, sun protection). An analysis of lifestyle factors and health behavior among *TP53* carriers suggested that women with a *TP53* carriers have healthier diet and smoked less compared to their relatives although no difference was observed in physical activity [97].

Other components of survivorship care in *TP53* carriers should be acknowledged. Survivorship trajectory of cancer patients is made not only by surveillance of recurrence and second primary malignancies but also by dealing with physical effects of cancer and chronic medical conditions, psychological effects and its social, work and financial implications [98].

Spectrum of *TP53* alterations and testing diagnostic perspective

In case a *TP53* pathogenic variant with minor allele frequency is

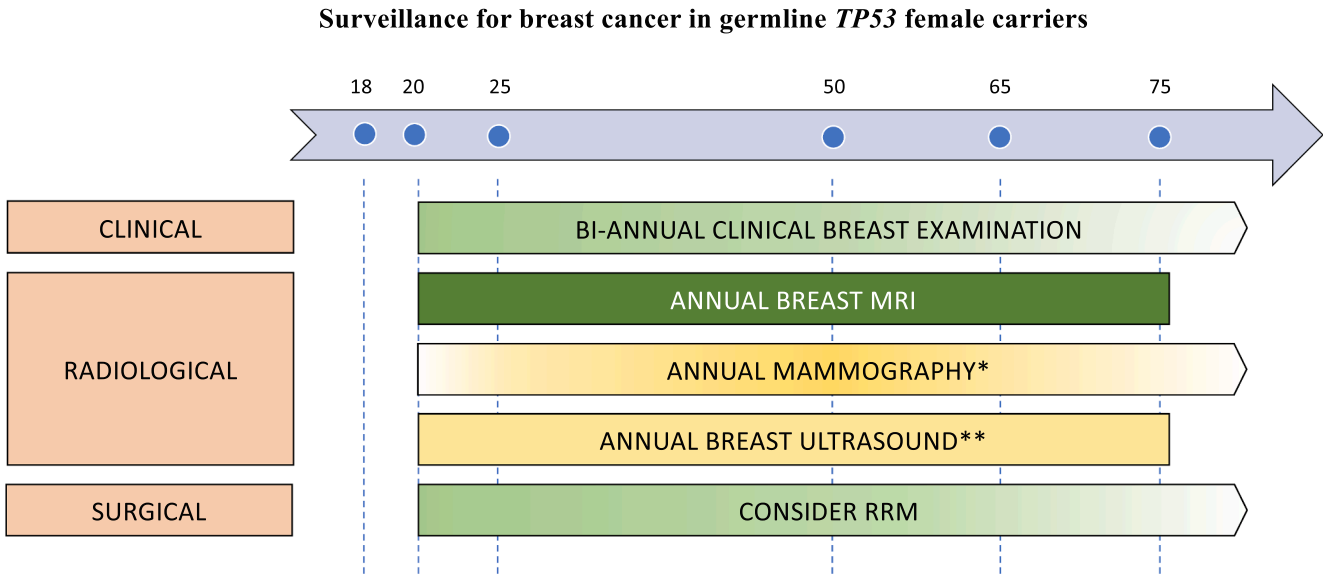

Fig. 1. Surveillance for breast cancer in germline *TP53* female carriers.
Dark green indicates high agreement, light green indicates medium agreement and yellow indicates very low agreement between guidelines
Filled arrows indicate agreement on the timing of examinations recommended between guidelines
Shaded arrows indicate discordance on the timing of examinations recommended between guidelines
*To be considered in case the MRI could not be performed. Recommended only by NCCN guidelines and by the TORONTO protocol. Attention should be paied to radiation-induced malignancies.
**as indicated by breast density
Footnote: no universal recomendation for mammography and breast ultrasound

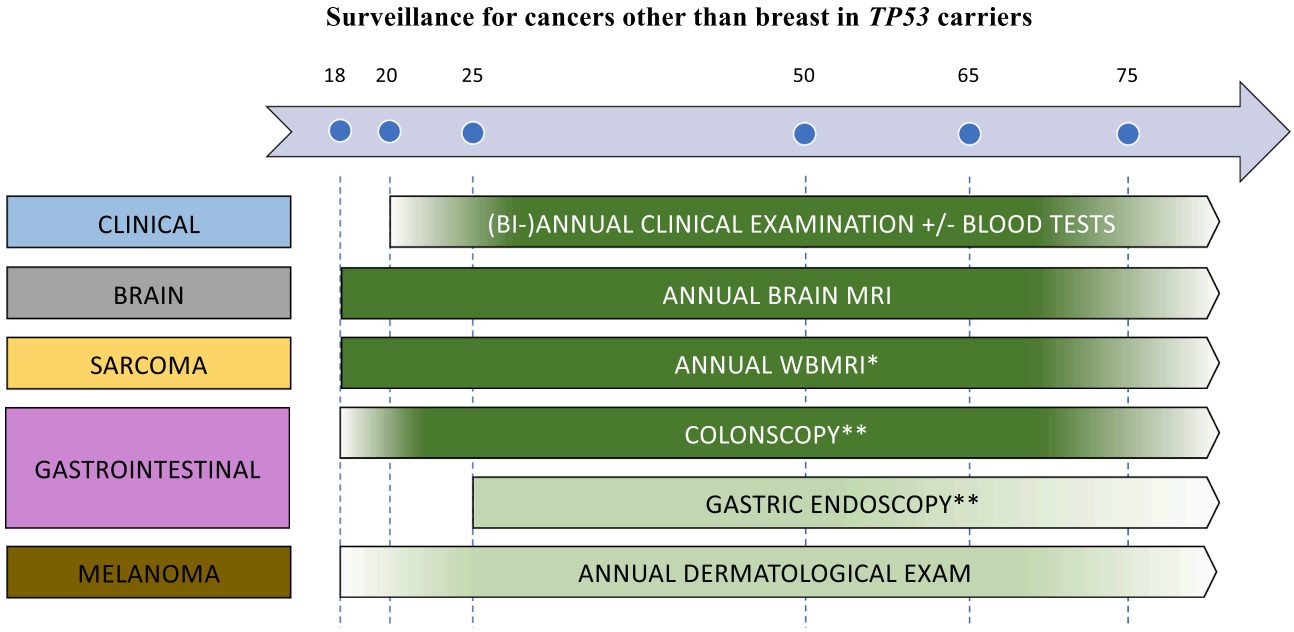

Fig. 2. Surveillance for cancers other than breast in *TP53* carriers.
Dark green indicates high agreement, light green indicates medium agreement
Filled arrows indicate agreement on the timing of examinations recommended between guidelines
Shaded arrows indicate discordance on the timing of examinations recommended between guidelines
* Annual WBMRI can be alternated to annual US of abdomen and pelvis (one radiological evaluation performed every 6 months)
** every 2–5 years. Recommended if the carrier received abdominal radiotherapy or if there is a family history of upper GI and/or colorectal tumors

found, mosaicism and clonal hematopoiesis should be considered. Pathogenic variants are assumed to be of germline origin when the allele frequency is approximately 50%; however, low variant allele frequencies (i.e., < 25–35%) might be found in a genetic report. In this case, minor allele frequency pathogenic variant is the result of a mutational event happened at a post-zygotic stage thus only tissues derived from the mutated cell will carry the pathogenic variant [99]. If the mutation is restricted to the hematopoietic compartment, it is called clonal hematopoiesis. Large cohort studies have demonstrated that the prevalence of clonal hematopoiesis increases with age and that clonal

hematopoiesis can be found in a significant portion of the healthy population [100–103]. Clonal hematopoiesis has most frequently been reported with *TP53* gene compared to other breast cancer susceptibility gene [99]. Thus, in case of detection of minor allele frequency *TP53* pathogenic variant the possibility of mosaicism should be ruled out as in this case different therapeutic and genetic counselling needs are implicated [99].

Identification of a *TP53* pathogenic variant does not always translate into the diagnosis of Li-Fraumeni syndrome. The different pathogenic variants can have different penetrance and thus different phenotypes. A pathogenic variant with reduced penetrance will possibly lead to an older age of occurrence of cancers of the Li-Fraumeni syndrome spectrum. For example, the funder mutation p.R181C in the *TP53* gene was found among 9 out of 453 Palestinian young women with breast cancer. None of the families that harbored the *TP53* p.R181C likely pathogenic variant fulfilled the clinical criteria for Li-Fraumeni syndrome[104]. Similarly, the penetrance of the p.R337H *TP53* pathogenic variant seem to be incomplete. In Southern Brazil, the population prevalence of *TP53* p.R337H pathogenic variant is 0.3%. In the Brazilian population, this variant seems to be associated with adrenocortical tumors in children but not with other cancers typical of the Li-Fraumeni syndrome [105–107].

Understanding the factors that lead to phenotypic differences among *TP53* carries is important to tailor the surveillance program and counselling. The classification of the Li-Fraumeni spectrum suggested by Kratz and colleagues seem to be a valid approach to classify the different phenotypic spectrums of *TP53* variants [108]. Authors classified germline *TP53* variants of 3034 persons into: phenotypic Li-Fraumeni syndrome (i.e., absence of a pathogenic/likely pathogenic *TP53* variant in person meeting clinical Li-Fraumeni syndrome criteria), Li-Fraumeni syndrome (i.e, presence of a pathogenic/likely pathogenic *TP53* variant in person meeting Li-Fraumeni syndrome testing criteria), attenuated Li-Fraumeni syndrome (i.e., presence of a pathogenic/likely pathogenic *TP53* variant in a person with cancer who does not meet Li-Fraumeni syndrome testing criteria), incidental Li-Fraumeni syndrome (i.e, presence of a pathogenic/likely pathogenic *TP53* variant in a person without a history of cancer). Results showed that patients who met Li-Fraumeni syndrome genetic testing criteria have more frequently early adrenal, brain, connective tissue, or bone tumors. While carriers who did not meet Li-Fraumeni syndrome genetic testing criteria had more breast and other cancers (45% of them occurring after age 45 years) [108].

Identification of germline *TP53* pathogenic variants in a breast cancer individual triggers cascade genetic testing of relatives (including children) for early diagnosis through increased surveillance and prevention. As the information regarding the identification of a pathogenic variant in the family relies in proband (proband-mediated procedure), it is uncertain whether all eligible relatives access testing. To our knowledge, no results on the uptake of *TP53* testing among at-risk family members are available. Moreover, testing of asymptomatic children at risk of Li Fraumeni syndrome remained controversial for a long time, due to the lack of proven medical benefit of screening, concern about informed consent and potential stigmatization and discrimination towards the minor [109]. However, due to emerging screening protocols showing potential efficacy, testing of at-risk children is becoming more widespread in those institutions where access to whole-body MRI is available [89,94]. Nevertheless, future research should also focus on the long-term clinical and psychosocial impacts of *TP53* genetic testing and early detection of such pathogenic variants in minors.

Finally, among young carriers of a pathogenic variant in breast cancer susceptibly genes, further burden is given by family planning with the 50% risk of transmission of the pathogenic variant to the offspring. Thus, current guidelines recommend that *TP53* carriers should be offered preimplantation genetic testing (in the case of in vitro fertilization) or prenatal diagnosis (in case of natural conception) [110,111]. However, barriers to the uptake of these techniques are similar to the ones faced by *BRCA* carriers and include the lack of availability and high cost of the procedure, ethical regulations and burden of additional psychological distress [110]. To our knowledge, no information is available regarding awareness, acceptance, and uptake of preimplantation genetic testing and prenatal testing among *TP53* carriers.

Conclusions

In patients with breast cancer, the prevalence of patients with germline pathogenic variants in *TP53* ranges from <0.5% in unselected patients with breast cancer to around 5–10% in highly selected patients with breast cancer such as those with very young age at diagnosis or with strong family history. Regarding locoregional treatment, current guidelines recommend that radiotherapy should be avoided and mastectomy should be preferred to lumpectomy [27,78,79]. Moreover, risk-reducing contralateral mastectomy should be discussed, and annual breast MRI screening is recommended as secondary prevention [27,78,79]. Whole-body MRI should be used for secondary cancer surveillance. No information is available regarding potential differences in treatment efficacy and indications among *TP53* carriers. Considering their potential worse breast cancer prognosis and risk of developing secondary malignancies, special attention should be paid to signs or symptoms suggesting the occurrence of these events.

The identification of a *TP53* pathogenic variant is not a straightforward to the diagnosis of Li-Fraumeni syndrome as different penetrance and phenotypes are present. No information on the uptake of cascade testing to at-risk family individuals is available and limited evidence exist on the implication of genetic testing in minors. Current guidelines recommend that preimplantation genetic testing and prenatal testing should be offered to patients willing to conceive [110,111]. Finally, the identification of a minor allele frequency of pathogenic variant needs further evaluations to rule out the possibility of mosaicism that can affect both cascade testing and preimplantation and prenatal testing.

Considering the limited data available to counsel patients with breast cancer and germline *TP53* pathogenic variants, the low level of evidence on some of the topic presented, the relatively rarity of this condition, and the interpretation of *TP53* found in the blood for other reason (e.g. clonal hematopoiesis and mosaicism), collaborative research efforts are strongly encouraged in order to provide more solid answers to improve and better tailor the care of this special patient population.

CRediT authorship contribution statement

Eva Blondeaux: Conceptualization, Writing – original draft, Writing – review & editing, Funding acquisition. **Luca Arecco:** Writing – review & editing, Visualization. **Kevin Punie:** Writing – review & editing, Visualization, Supervision. **Rossella Graffeo:** Writing – review & editing, Visualization, Supervision. **Angela Toss:** Writing – review & editing, Visualization, Supervision. **Carmine De Angelis:** Writing – review & editing, Visualization, Supervision. **Lucia Trevisan:** Writing – review & editing, Visualization. **Giulia Buzzatti:** Writing – review & editing, Visualization. **Sabine C. Linn:** Writing – review & editing, Visualization, Supervision. **Peter Dubsky:** Writing – review & editing, Visualization, Supervision. **Mara Cruellas:** Writing – review & editing, Visualization. **Ann H. Partridge:** Writing – review & editing, Visualization, Supervision. **Judith Balmaña:** Writing – review & editing, Visualization, Supervision. **Shani Paluch-Shimon:** Writing – review & editing, Visualization, Supervision. **Matteo Lambertini:** Conceptualization, Writing – original draft, Writing – review & editing, Visualization, Supervision.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: ‘**Eva Blondeaux** reports research grant (to the Institution) from Gilead

to pursue research effort in the field of TP53 pathogenic variants. **Kevin Punie** reports honoraria for consultancy/advisory roles from Astra Zeneca, Eli Lilly, Exact Sciences, Focus Patient, Gilead Sciences, MSD, Novartis, Pfizer, Roche, Seagen; honoraria for consultancy/advisory roles paid to my institution from Astra Zeneca, Eli Lilly, Exact Sciences, Gilead, MSD, Novartis, Pfizer, Roche, Seagen. Research funding paid to my institution from Sanofi and MSD. Stock options: Need Inc. Travel support: Astra Zeneca, Novartis, Pfizer, PharmaMar, Roche. **Carmine De Angelis** reports advisory role for Roche, Lilly, Novartis, Astrazeneca, Pfizer, Seagen, Gilead, and GSK and speaker honoraria from Roche, Lilly, Novartis, Pfizer, Seagen, and GSK, Travel Grants from Gilead and research support (to the Institution) from Novartis outside the submitted work. **Sabine C. Linn** reports an advisory role for AstraZeneca and Daiichi Sankyo Europe GmbH (paid to the institution), travel and accommodation expenses from Daiichi Sankyo Europe GmbH, and research support (to the institution) from Genentech/Roche, AstraZeneca, Bristol Myers Squibb, Tesaro (now GSK), Merck, Immunomedics (now Gilead), Eurocept Pharmaceuticals, Agendia, and Novartis. **Mara Cruellas** reports speaker honoraria from Roche and Astrazeneca. **Shani Paluch-Shimon** reports - advisory Board consultancy, speaker's bureau: AstraZeneca, Pfizer, Novartis, Lilly, Roche, MSD, Exact Sciences. Gilead. Travel: Roche. Research Funding: Pfizer. **Matteo Lambertini** reports advisory role for Roche, Lilly, Novartis, Astrazeneca, Pfizer, Seagen, Gilead, MSD and Exact Sciences and speaker honoraria from Roche, Lilly, Novartis, Pfizer, Sandoz, Libbs, Daiichi Sankyo and Takeda, Travel Grants from Gilead and research support (to the Institution) from Gilead outside the submitted work. All the other authors declare no conflict of interest.'

Acknowledgment

Funding: The project was partially funded by a Gilead Sciences Medical Grant (Fellowship Program 2022) (no grant number).

ROLE OF THE FUNDING SOURCE

The funding source was not involved in conceptualization, in the writing of the manuscript; and in the decision to submit the article for publication

References

[1] Rosenberg SM, Newman LA, Partridge AH. Breast cancer in young women: rare disease or public health problem? JAMA Oncol 2015;1(7):877–8.
[2] Euhus DM. Understanding mathematical models for breast cancer risk assessment and counseling. Breast J 2001;7(4):224–32.
[3] Tung N, Lin NU, Kidd J, Allen BA, Singh N, Wenstrup RJ, et al. Frequency of germline mutations in 25 cancer susceptibility genes in a sequential series of patients with breast cancer. J Clin Oncol Off J Am Soc Clin Oncol 2016;34(13):1460–8.
[4] Pharoah PDP, Dunning AM, Ponder BAJ, Easton DF. Association studies for finding cancer-susceptibility genetic variants. Nat Rev Cancer 2004;4(11):850–60.
[5] Breast Cancer Association Consortium, Dorling L, Carvalho S, Allen J, González-Neira A, Luccarini C, et al. Breast Cancer Risk Genes — Association Analysis in More than 113,000 Women. N Engl J Med. 2021;384(5):428–39.
[6] Hu C, Hart SN, Gnanaolivu R, Huang H, Lee KY, Na J, et al. A population-based study of genes previously implicated in breast cancer. N Engl J Med 2021;384(5):440–51.
[7] Olivier M, Hollstein M, Hainaut P. TP53 mutations in human cancers: origins, consequences, and clinical use. Cold Spring Harb Perspect Biol 2010;2(1):a001008.
[8] Sheng S, Xu Y, Guo Y, Yao L, Hu L, Ouyang T, et al. Prevalence and clinical impact of TP53 germline mutations in Chinese women with breast cancer. Int J Cancer 2020;146(2):487–95.
[9] Li FP, Fraumeni JF. Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? Ann Intern Med 1969;71(4):747–52.
[10] Wasserman JD, Novokmet A, Eichler-Jonsson C, Ribeiro RC, Rodriguez-Galindo C, Zambetti GP, et al. Prevalence and functional consequence of TP53 mutations in pediatric adrenocortical carcinoma: a children's oncology group study. J Clin Oncol Off J Am Soc Clin Oncol 2015;33(6):602–9.
[11] Zhang J, Walsh MF, Wu G, Edmonson MN, Gruber TA, Easton J, et al. Germline mutations in predisposition genes in pediatric cancer. N Engl J Med 2015;373(24):2336–46.
[12] Amadou A, Achatz MIW, Hainaut P. Revisiting tumor patterns and penetrance in germline TP53 mutation carriers: temporal phases of Li-Fraumeni syndrome. Curr Opin Oncol 2018;30(1):23–9.
[13] Maxwell KN, Cheng HH, Powers J, Gulati R, Ledet EM, Morrison C, et al. Inherited TP53 variants and risk of prostate cancer. Eur Urol 2022;81(3):243–50.
[14] Lustbader ED, Williams WR, Bondy ML, Strom S, Strong LC. Segregation analysis of cancer in families of childhood soft-tissue-sarcoma patients. Am J Hum Genet 1992;51(2):344–56.
[15] Wu CC, Shete S, Amos CI, Strong LC. Joint effects of germ-line p53 mutation and sex on cancer risk in Li-Fraumeni syndrome. Cancer Res 2006;66(16):8287–92.
[16] Fang S, Krahe R, Bachinski LL, Zhang B, Amos CI, Strong LC. Sex-specific effect of the TP53 PIN3 polymorphism on cancer risk in a cohort study of TP53 germline mutation carriers. Hum Genet 2011;130(6):789–94.
[17] Hwang SJ, Lozano G, Amos CI, Strong LC. Germline p53 mutations in a cohort with childhood sarcoma: sex differences in cancer risk. Am J Hum Genet 2003;72(4):975–83.
[18] Evans DGR, Birch JM, Ramsden RT, Sharif S, Baser ME. Malignant transformation and new primary tumours after therapeutic radiation for benign disease: substantial risks in certain tumour prone syndromes. J Med Genet 2006;43(4):289–94.
[19] Schon K, Tischkowitz M. Clinical implications of germline mutations in breast cancer: TP53. Breast Cancer Res Treat 2018;167(2):417–23.
[20] Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, et al. Risks of breast, ovarian, and contralateral breast cancer for *BRCA1* and *BRCA2* mutation carriers. JAMA 2017;317(23):2402.
[21] 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(23):3673–81.
[22] Li FP, Fraumeni JF, Mulvihill JJ, Blattner WA, Dreyfus MG, Tucker MA, et al. A cancer family syndrome in twenty-four kindreds. Cancer Res 1988;48(18):5358–62.
[23] Birch JM, Hartley AL, Tricker KJ, Prosser J, Condie A, Kelsey AM, et al. Prevalence and diversity of constitutional mutations in the p53 gene among 21 Li-Fraumeni families. Cancer Res 1994;54(5):1298–304.
[24] Eeles RA. Germline mutations in the TP53 gene. Cancer Surv 1995;25:101–24.
[25] Chompret A, Abel A, Stoppa-Lyonnet D, Brugiéres L, Pagés S, Feunteun J, et al. Sensitivity and predictive value of criteria for p53 germline mutation screening. J Med Genet 2001;38(1):43–7.
[26] Bougeard G, Renaux-Petel M, Flaman JM, Charbonnier C, Fermey P, Belotti M, et al. Revisiting Li-Fraumeni syndrome from TP53 mutation carriers. J Clin Oncol Off J Am Soc Clin Oncol 2015;33(21):2345–52.
[27] Frebourg T, Bajalica Lagercrantz S, Oliveira C, Magenheim R, Evans DG, Network ER, et al. Guidelines for the Li-Fraumeni and heritable TP53-related cancer syndromes. Eur J Hum Genet EJHG 2020;28(10):1379–86.
[28] Evans DG, Woodward ER, Bajalica-Lagercrantz S, Oliveira C, Frebourg T. Germline TP53 testing in breast cancers: why, when and how? Cancers 2020;12(12):E3762.
[29] Tinat J, Bougeard G, Baert-Desurmont S, Vasseur S, Martin C, Bouvignies E, et al. 2009 version of the Chompret criteria for Li Fraumeni syndrome. J Clin Oncol Off J Am Soc Clin Oncol. 2009;27(26):e108–109; author reply e110.
[30] Gonzalez KD, Noltner KA, Buzin CH, Gu D, Wen-Fong CY, Nguyen VQ, et al. Beyond Li Fraumeni syndrome: clinical characteristics of families with p53 germline mutations. J Clin Oncol Off J Am Soc Clin Oncol 2009;27(8):1250–6.
[31] Ruijs MWG, Verhoef S, Rookus MA, Pruntel R, van der Hout AH, Hogervorst FBL, et al. TP53 germline mutation testing in 180 families suspected of Li-Fraumeni syndrome: mutation detection rate and relative frequency of cancers in different familial phenotypes. J Med Genet 2010;47(6):421–8.
[32] Renaux-Petel M, Charbonnier F, Théry JC, Fermey P, Lienard G, Bou J, et al. Contribution of de novo and mosaic TP53 mutations to Li-Fraumeni syndrome. J Med Genet 2018;55(3):173–80.
[33] Bakhuizen JJ, Hogervorst FB, Velthuizen ME, Ruijs MW, van Engelen K, van Os TA, et al. TP53 germline mutation testing in early-onset breast cancer: findings from a nationwide cohort. Fam Cancer 2019;18(2):273–80.
[34] Breast Cancer Association Consortium, Mavaddat N, Dorling L, Carvalho S, Allen J, González-Neira A, et al. Pathology of Tumors Associated With Pathogenic Germline Variants in 9 Breast Cancer Susceptibility Genes. JAMA Oncol. 2022;8(3):e216744.
[35] Evans DGR, Birch JM, Thorneycroft M, McGown G, Lalloo F, Varley JM. Low rate of TP53 germline mutations in breast cancer/sarcoma families not fulfilling classical criteria for Li-Fraumeni syndrome. J Med Genet 2002;39(12):941–4.
[36] Walsh T, Casadei S, Coats KH, Swisher E, Stray SM, Higgins J, et al. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. JAMA 2006;295(12):1379–88.
[37] Lalloo F, Varley J, Moran A, Ellis D, O'dair L, Pharoah P, et al. BRCA1, BRCA2 and TP53 mutations in very early-onset breast cancer with associated risks to relatives. Eur J Cancer Oxf Engl 1990. 2006;42(8):1143–50.
[38] Manoukian S, Peissel B, Pensotti V, Barile M, Cortesi L, Stacchiotti S, et al. Germline mutations of TP53 and BRCA2 genes in breast cancer/sarcoma families. Eur J Cancer Oxf Engl 2007;43(3):601–6.
[39] Ginsburg OM, Akbari MR, Aziz Z, Young R, Lynch H, Ghadirian P, et al. The prevalence of germ-line TP53 mutations in women diagnosed with breast cancer before age 30. Fam Cancer 2009;8(4):563–7.
[40] Mouchawar J, Korch C, Byers T, Pitts TM, Li E, McCredie MRE, et al. Population-based estimate of the contribution of TP53 mutations to subgroups of early-onset breast cancer: Australian Breast Cancer Family Study. Cancer Res 2010;70(12):4795–800.

[41] Lee DSC, Yoon SY, Looi LM, Kang P, Kang IN, Sivanandan K, et al. Comparable frequency of BRCA1, BRCA2 and TP53 germline mutations in a multi-ethnic Asian cohort suggests TP53 screening should be offered together with BRCA1/2 screening to early-onset breast cancer patients. Breast Cancer Res BCR 2012;14 (2):R66.

[42] McCuaig JM, Armel SR, Novokmet A, Ginsburg OM, Demsky R, Narod SA, et al. Routine TP53 testing for breast cancer under age 30: ready for prime time? Fam Cancer 2012;11(4):607–13.

[43] 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(1):193–8.

[44] Carraro DM, Koike Folgueira MAA, Garcia Lisboa BC, Ribeiro Olivieri EH, Vitorino Krepischi AC, de Carvalho AF, et al. Comprehensive analysis of BRCA1, BRCA2 and TP53 germline mutation and tumor characterization: a portrait of early-onset breast cancer in Brazil. PLoS One 2013;8(3):e57581.

[45] Eccles DM, Li N, Handwerker R, Maishman T, Copson ER, Durcan LT, et al. Genetic testing in a cohort of young patients with HER2-amplified breast cancer. Ann Oncol Off J Eur Soc Med Oncol 2016;27(3):467–73.

[46] Hahn EC, Bittar CM, Vianna FSL, Netto CBO, Biazús JV, Cericatto R, et al. TP53 p. Arg337His germline mutation prevalence in Southern Brazil: further evidence for mutation testing in young breast cancer patients. PloS One 2018;13(12): e0209934.

[47] Gallardo-Alvarado LN, Tusié-Luna MT, Tussié-Luna MI, Díaz-Chávez J, Segura YX, Bargallo-Rocha E, et al. Prevalence of germline mutations in the TP53 gene in patients with early-onset breast cancer in the Mexican population. BMC Cancer 2019;19(1):118.

[48] Rogoża-Janiszewska E, Malińska K, Górski B, Scott RJ, Cybulski C, Kluźniak W, et al. Prevalence of germline TP53 variants among early-onset breast cancer patients from Polish population. Breast Cancer Tokyo Jpn 2021;28(1):226–35.

[49] Siraj AK, Masoodi T, Bu R, Parvathareddy SK, Iqbal K, Azam S, et al. Prevalence of germline TP53 mutation among early onset middle eastern breast cancer patients. Hered Cancer Clin Pract 2021;19(1):49.

[50] Waks AG, Kim D, Jain E, Snow C, Kirkner GJ, Rosenberg SM, et al. Somatic and germline genomic alterations in very young women with breast cancer. Clin Cancer Res Off J Am Assoc Cancer Res 2022;28(11):2339–48.

[51] Arcand SL, Akbari MR, Mes-Masson AM, Provencher D, Foulkes WD, Narod SA, et al. Germline TP53 mutational spectrum in French Canadians with breast cancer. BMC Med Genet 2015;12(16):24.

[52] Arcand SL, Maugard CM, Ghadirian P, Robidoux A, Perret C, Zhang P, et al. Germline TP53 mutations in BRCA1 and BRCA2 mutation-negative French Canadian breast cancer families. Breast Cancer Res Treat 2008;108(3):399–408.

[53] Lalloo F, Varley J, Ellis D, Moran A, O'Dair L, Pharoah P, et al. Prediction of pathogenic mutations in patients with early-onset breast cancer by family history. Lancet Lond Engl 2003;361(9363):1101–2.

[54] Rana HQ, Gelman R, LaDuca H, McFarland R, Dalton E, Thompson J, et al. Differences in TP53 mutation carrier phenotypes emerge from panel-based testing. J Natl Cancer Inst 2018;110(8):863–70.

[55] Fortuno C, James PA, Spurdle AB. Current review of TP53 pathogenic germline variants in breast cancer patients outside Li-Fraumeni syndrome. Hum Mutat 2018;39(12):1764–73.

[56] 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(11):771–4.

[57] 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(4):908–13.

[58] 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 Jun;133(3):1125–30.

[59] 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(3):189–98.

[60] Le AN, Harton J, Desai H, Powers J, Zelley K, Bradbury AR, et al. Frequency of radiation-induced malignancies post-adjuvant radiotherapy for breast cancer in patients with Li-Fraumeni syndrome. Breast Cancer Res Treat 2020;181(1): 181–8.

[61] Alyami H, Yoo TK, Cheun JH, Lee HB, Jung SM, Ryu JM, et al. Clinical features of breast cancer in South Korean patients with germline TP53 gene mutations. J Breast Cancer 2021;24(2):175–82.

[62] Kuba MG, Lester SC, Bowman T, Stokes SM, Taneja KL, Garber JE, et al. Histopathologic features of breast cancer in Li-Fraumeni syndrome. Mod Pathol Off J U S Can Acad Pathol Inc. 2021;34(3):542–8.

[63] Rippinger N, Fischer C, Sinn HP, Dikow N, Sutter C, Rhiem K, et al. Breast cancer characteristics and surgery among women with Li-Fraumeni syndrome in Germany-A retrospective cohort study. Cancer Med 2021;10(21):7747–58.

[64] Sandoval RL, Polidorio N, Leite ACR, Cartaxo M, Pisani JP, Quirino CV, et al. Breast cancer phenotype associated with Li-Fraumeni syndrome: a brazilian cohort enriched by TP53 p.R337H carriers. Front Oncol. 2022;12:836937.

[65] Sjögren S, Inganäs M, Lindgren A, Holmberg L, Bergh J. Prognostic and predictive value of c-erbB-2 overexpression in primary breast cancer, alone and in combination with other prognostic markers. J Clin Oncol Off J Am Soc Clin Oncol 1998;16(2):462–9.

[66] Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LAG, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst. 2014;106(5):dju055.

[67] Langerød A, Zhao H, Borgan Ø, Nesland JM, Bukholm IRK, Ikdahl T, et al. TP53 mutation status and gene expression profiles are powerful prognostic markers of breast cancer. Breast Cancer Res BCR 2007;9(3):R30.

[68] Shahbandi A, Nguyen HD, Jackson JG. TP53 mutations and outcomes in breast cancer: reading beyond the headlines. Trends Cancer 2020;6(2):98–110.

[69] Eikesdal HP, Knappskog S, Aas T, Lønning PE. TP53 status predicts long-term survival in locally advanced breast cancer after primary chemotherapy. Acta Oncol Stockh Swed 2014;53(10):1347–55.

[70] Andersson J, Larsson L, Klaar S, Holmberg L, Nilsson J, Inganäs M, et al. Worse survival for TP53 (p53)-mutated breast cancer patients receiving adjuvant CMF. Ann Oncol Off J Eur Soc Med Oncol 2005;16(5):743–8.

[71] Guo Y, Wan Q, Ouyang T, Li J, Wang T, Fan Z, et al. Risk of ipsilateral breast tumor recurrence and contralateral breast cancer in patients with and without TP53 variant in a large series of breast cancer patients. Breast 2022;1(65):55–60.

[72] Hyder Z, Harkness EF, Woodward ER, Bowers NL, Pereira M, Wallace AJ, et al. Risk of contralateral breast cancer in women with and without pathogenic variants in BRCA1, BRCA2, and TP53 genes in women with very early-onset (<36 years) breast cancer. Cancers 2020;12(2):E378.

[73] Petry V, Bonadio RC, Cagnacci AQC, Senna LAL, Campos R do NG, Cotti GC, et al. Radiotherapy-induced malignancies in breast cancer patients with TP53 pathogenic germline variants (Li-Fraumeni syndrome). Fam Cancer 2020;19(1): 47–53.

[74] Heymann S, Delaloge S, Rahal A, Caron O, Frebourg T, Barreau L, et al. Radio-induced malignancies after breast cancer postoperative radiotherapy in patients with Li-Fraumeni syndrome. Radiat Oncol Lond Engl 2010;8(5):104.

[75] Nandikolla AG, Venugopal S, Anampa J. Breast cancer in patients with Li-Fraumeni syndrome - a case-series study and review of literature. Breast Cancer Dove Med Press 2017;9:207–15.

[76] Kappel S, Janschek E, Wolf B, Rudas M, Teleky B, Jakesz R, et al. TP53 germline mutation may affect response to anticancer treatments: analysis of an intensively treated Li-Fraumeni family. Breast Cancer Res Treat 2015;151(3):671–8.

[77] Varley JM, McGown G, Thorncroft M, James LA, Margison GP, Forster G, et al. Are there low-penetrance TP53 Alleles? Evidence from childhood adrenocortical tumors. Am J Hum Genet 1999;65(4):995–1006.

[78] Sessa C, Balmaña J, Bober SL, Cardoso MJ, Colombo N, Curigliano G, et al. Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes: ESMO Clinical Practice Guideline. Ann Oncol 2022. S092375342204193X.

[79] Tung NM, Boughey JC, Pierce LJ, Robson ME, Bedrosian I, Dietz JR, et al. Management of hereditary breast cancer: American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Guideline. J Clin Oncol Off J Am Soc Clin Oncol 2020;38(18):2080–106.

[80] Daly MB, Pal T, Berry MP, Buys SS, Dickson P, Domchek SM, et al. Genetic/familial high-risk assessment: breast, ovarian, and pancreatic, version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw JNCCN 2021;19(1):77–102.

[81] Davey MG, Davey CM, Ryan ÉJ, Lowery AJ, Kerin MJ. Combined breast conservation therapy versus mastectomy for BRCA mutation carriers – A systematic review and meta-analysis. Breast 2021;56:26–34.

[82] Giannakeas V, Narod SA. The expected benefit of preventive mastectomy on breast cancer incidence and mortality in BRCA mutation carriers, by age at mastectomy. Breast Cancer Res Treat 2018;167(1):263–7.

[83] Kasper E, Angot E, Colasse E, Nicol L, Sabourin JC, Adriouch S, et al. Contribution of genotoxic anticancer treatments to the development of multiple primary tumours in the context of germline TP53 mutations. Eur J Cancer Oxf Engl 2018; 1990(101):254–62.

[84] Teepen JC, van Leeuwen FE, Tissing WJ, van Dulmen-den BE, van den Heuvel-Eibrink MM, van der Pal HJ, et al. Long-term risk of subsequent malignant neoplasms after treatment of childhood cancer in the DCOG LATER study cohort: role of chemotherapy. J Clin Oncol Off J Am Soc Clin Oncol 2017;35(20): 2288–98.

[85] Gruber JJ, Afghahi A, Timms K, DeWees A, Gross W, Aushev VN, et al. A phase II study of talazoparib monotherapy in patients with wild-type BRCA1 and BRCA2 with a mutation in other homologous recombination genes. Nat Cancer 2022;3 (10):1181–91.

[86] Tung NM, Robson ME, Ventz S, Santa-Maria CA, Nanda R, Marcom PK, et al. TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes. J Clin Oncol [Internet]. 2020 Oct 29 [cited 2022 Oct 26]; Available from: https://ascopubs.org/doi/pdf/10.1200/JCO.20.02151?role=tab.

[87] Kumamoto T, Yamazaki F, Nakano Y, Tamura C, Tashiro S, Hattori H, et al. Medical guidelines for Li-Fraumeni syndrome 2019, version 1.1. Int J Clin Oncol 2021;26(12):2161–78.

[88] Hanson H, Brady AF, Crawford G, Eeles RA, Gibson S, Jorgensen M, et al. UKCGG Consensus Group guidelines for the management of patients with constitutional TP53 pathogenic variants. J Med Genet. 2020;jmedgenet-2020-106876.

[89] Villani A, Shore A, Wasserman JD, Stephens D, Kim RH, Druker H, et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study. Lancet Oncol 2016;17(9):1295–305.

[90] Kratz CP, Achatz MI, Brugières L, Frebourg T, Garber JE, Greer MLC, et al. Cancer screening recommendations for individuals with Li-Fraumeni syndrome. Clin Cancer Res Off J Am Assoc Cancer Res 2017;23(11):e38–45.

[91] Paluch-Shimon S, Cardoso F, Partridge AH, Abulkhair O, Azim HA, Bianchi-Micheli G, et al. ESO-ESMO 5th international consensus guidelines for breast cancer in young women (BCY5). Ann Oncol Off J Eur Soc Med Oncol. 2022; S0923-7534(22)01858-0.

[92] 749-TP53 (Li-Fraumeni) – risk management (adult) | eviQ [Internet]. [cited 2022 Dec 5]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/749-tp53-li-fraumeni-risk-management-adult.
[93] Saya S, Killick E, Thomas S, Taylor N, Bancroft EK, Rothwell J, et al. Baseline results from the UK SIGNIFY study: a whole-body MRI screening study in TP53 mutation carriers and matched controls. Fam Cancer 2017;16(3):433–40.
[94] Ballinger ML, Best A, Mai PL, Khincha PP, Loud JT, Peters JA, et al. Baseline surveillance in Li-Fraumeni syndrome using whole-body magnetic resonance imaging: a meta-analysis. JAMA Oncol 2017;3(12):1634–9.
[95] Petralia G, Padhani AR. Whole-body magnetic resonance imaging in oncology: uses and indications. Magn Reson Imaging Clin N Am 2018;26(4):495–507.
[96] Omran M, Blomqvist L, Brandberg Y, Pal N, Kogner P, Ståhlbom AK, et al. Whole-body MRI within a surveillance program for carriers with clinically actionable germline TP53 variants - the Swedish constitutional TP53 study SWEP53. Hered Cancer Clin Pract 2020;13(18):1.
[97] Nees J, Kiermeier S, Struewe F, Keymling M, Maatouk I, Kratz CP, et al. Health behavior and cancer prevention among adults with Li-Fraumeni syndrome and relatives in Germany-A cohort description. Curr Oncol Tor Ont 2022;29(10):7768–78.
[98] Vaz-Luis I, Masiero M, Cavaletti G, Cervantes A, Chlebowski RT, Curigliano G, et al. ESMO Expert Consensus Statements on Cancer Survivorship: promoting high-quality survivorship care and research in Europe. Ann Oncol [Internet]. 2022 [cited 2022 Oct 25];0(0). Available from: https://www.annalsofoncology.org/article/S0923-7534(22)03792-9/fulltext.
[99] Batalini F, Peacock EG, Stobie L, Robertson A, Garber J, Weitzel JN, et al. Li-Fraumeni syndrome: not a straightforward diagnosis anymore-the interpretation of pathogenic variants of low allele frequency and the differences between germline PVs, mosaicism, and clonal hematopoiesis. Breast Cancer Res BCR 2019;21(1):107.
[100] Jacobs KB, Yeager M, Zhou W, Wacholder S, Wang Z, Rodriguez-Santiago B, et al. Detectable clonal mosaicism and its relationship to aging and cancer. Nat Genet 2012;44(6):651–8.
[101] Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman PV, Mar BG, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med 2014;371(26):2488–98.
[102] Xie M, Lu C, Wang J, McLellan MD, Johnson KJ, Wendl MC, et al. Age-related mutations associated with clonal hematopoietic expansion and malignancies. Nat Med 2014;20(12):1472–8.
[103] Genovese G, Kähler AK, Handsaker RE, Lindberg J, Rose SA, Bakhoum SF, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med 2014;371(26):2477–87.
[104] Lolas Hamameh S, Renbaum P, Kamal L, Dweik D, Salahat M, Jaraysa T, et al. Genomic analysis of inherited breast cancer among Palestinian women: Genetic heterogeneity and a founder mutation in TP53. Int J Cancer 2017;141(4):750–6.
[105] Giacomazzi J, Graudenz MS, Osorio CABT, Koehler-Santos P, Palmero EI, Zagonel-Oliveira M, et al. Prevalence of the TP53 p.R337H mutation in breast cancer patients in Brazil. PloS One 2014;9(6):e99893.
[106] Custódio G, Parise GA, Kiesel Filho N, Komechen H, Sabbaga CC, Rosati R, et al. Impact of neonatal screening and surveillance for the TP53 R337H mutation on early detection of childhood adrenocortical tumors. J Clin Oncol Off J Am Soc Clin Oncol 2013;31(20):2619–26.
[107] Sandoval RL, Masotti C, de Macedo MP, Ribeiro MFSA, Leite ACR, Meireles SI, et al. Identification of the TP53 p.R337H Variant in Tumor Genomic Profiling Should Prompt Consideration of Germline Testing for Li-Fraumeni Syndrome. JCO Glob Oncol. 2021;7:GO.21.00097.
[108] Kratz CP, Freycon C, Maxwell KN, Nichols KE, Schiffman JD, Evans DG, et al. Analysis of the Li-Fraumeni spectrum based on an international germline TP53 variant data set: an international agency for research on cancer TP53 database analysis. JAMA Oncol 2021;7(12):1800–5.
[109] Evans DG, Lunt P, Clancy T, Eeles R. Childhood predictive genetic testing for Li-Fraumeni syndrome. Fam Cancer 2010;9(1):65–9.
[110] Vuković P, Peccatori FA, Massarotti C, Miralles MS, Beketić-Orešković L, Lambertini M. Preimplantation genetic testing for carriers of BRCA1/2 pathogenic variants. Crit Rev Oncol Hematol 2021;157:103201.
[111] Paluch-Shimon S, Cardoso F, Sessa C, Balmana J, Cardoso MJ, Gilbert F, et al. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. Ann Oncol Off J Eur Soc Med Oncol 2016;27(suppl 5):v103–10.