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ORIGINAL ARTICLE

TP53 germline mutation testing in early-onset breast cancer: findings from a nationwide cohort

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Abstract

Early-onset breast cancer may be due to Li–Fraumeni Syndrome (LFS). Current national and international guidelines recommend that *TP53* genetic testing should be considered for women with breast cancer diagnosed before the age of 31 years. However, large studies investigating *TP53* mutation prevalence in this population are scarce. We collected nationwide laboratory records for all young breast cancer patients tested for *TP53* mutations in the Netherlands. Between 2005 and 2016, 370 women diagnosed with breast cancer younger than 30 years of age were tested for *TP53* germline mutations, and eight (2.2%) were found to carry a (likely) pathogenic *TP53* sequence variant. Among *BRCA1*/*BRCA2* mutation negative women without a family history suggestive of LFS or a personal history of multiple LFS-related tumours, the *TP53* mutation frequency was < 1% (2/233). Taking into consideration that *TP53* mutation prevalence was comparable or even higher in some studies selecting patients with breast cancer onset at older ages or HER2-positive breast cancers, raises the question of whether a very early age of onset is an appropriate single *TP53* genetic testing criterion.

Keywords Genetic testing · Li–Fraumeni syndrome · TP53 · Breast cancer · Hereditary

Introduction

Breast cancer is the most common cancer among women in the Netherlands, accounting for 28% of all newly diagnosed cancers in women in 2016 [1]. Although most cases of breast cancer are sporadic, an estimated 5–10% are attributable to inherited germline mutations in single genes, particularly the *BRCA1* or *BRCA2* genes [2, 3]. Since early onset of breast cancer is an indicator of genetic susceptibility [4], diagnostic *BRCA1*/*BRCA2* DNA testing is offered to all women diagnosed with breast cancer before the age of 40 (in the Netherlands) or 46 (in the U.S.A.) [5, 6]. In addition, routine parallel genetic testing for *CHEK2*1100delC* mutations has been performed in the Netherlands since September 2014 [7]. However, there are some other cancer predisposition genes that are associated with early-onset breast cancer, including *TP53*, which has been linked to Li Fraumeni syndrome (LFS) [6].

LFS is a rare autosomal dominant inherited cancer syndrome [8]. This syndrome is characterized by a high risk for a wide variety of early-onset neoplasms [9]. The National Cancer Institute showed a cumulative cancer incidence of

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50% by age 31 years among female *TP53* germline mutation carriers and an incidence of nearly 100% by age 70 years [10]. Sarcoma, breast cancer, brain tumours and adrenocortical carcinoma are the most frequently observed tumours in patients with germline *TP53* mutations [9, 11].

Over the years, several different sets of criteria have been established to identify individuals and families at risk for a germline *TP53* mutation [11–16]. The strictest criteria are the clinical criteria for classical LFS and Li–Fraumeni-like syndrome (LFL) [12–14]. However, *TP53* mutations were also identified in families who had not fulfilled these clinical criteria due to another tumour spectrum, age at diagnosis or sporadic occurrence of cancer [9, 11]. It is estimated that at least 14% of germline *TP53* mutation carriers have a de novo mutation [17]. Therefore, lack of a positive family history does not exclude the possibility of a *TP53* mutation. To cover the different clinical presentations of LFS, and to facilitate the identification of germline *TP53* mutations, Chompret and colleagues have sequentially updated the testing criteria [11, 16]. Recent multigene panel studies suggest that LFS may have a broader phenotypic spectrum than previously reported because *TP53* germline mutations have been identified in individuals who do not fulfill established clinical criteria recommended for LFS testing [18–20]. *TP53* mutation carriers detected by multigene panel testing (MGPT) are notably older at breast cancer diagnosis [18].

Breast cancer is the most frequently observed cancer in women with *TP53* germline mutations [21]. Several studies have described *TP53* germline mutations in women with early-onset breast cancer (age of diagnosis ≤ 30 years). Reported mutation detection rates varied between 0% and 8.5%, but these numbers are largely based on small studies [9, 11, 22–26]. In 2015, the Chompret *TP53* testing criteria were revised to include early-onset breast cancer [11]. In addition to an early age of onset, amplification of HER2 has been reported as more common in *TP53*-mutation-associated breast cancer [27–29].

According to the third (2005) and fourth (2010) edition of the Dutch national consensus-based guideline for genetics professionals (STOET/VKGN), *TP53* germline mutation testing could be considered in women with breast cancer diagnosed before the age of 30 [30, 31]. The latest guideline (2017) recommends *TP53* genetic testing in all breast cancer patients diagnosed before the age of 31, following the 2015 version of the Chompret criteria [32]. We conducted a nationwide retrospective laboratory records review in order to evaluate the prevalence of *TP53* germline mutations among early-onset breast cancer patients in the Netherlands. We also examined genetics professionals' experiences and attitudes regarding the timing and content of genetic counselling for LFS. The results of this survey have been published [33]. Our overall aim is to gain insight into the genetic counselling and testing of young breast cancer patients for LFS in order to make clinical recommendations regarding the most appropriate counselling strategy for these women.

Methods

Subjects

We retrospectively reviewed the laboratory records of all women diagnosed with invasive breast cancer or carcinoma in situ before the age of 30 who had been tested for *TP53* germline mutations in the Netherlands between January 2005 and December 2016. Patients were referred for *TP53* genetic testing on the basis of eligibility criteria that were part of the national guidelines of that time [30, 31]. In the Netherlands, *TP53* mutation analysis is performed in six DNA-diagnostics laboratories. Early-onset breast cancer patients were identified by checking the *TP53* DNA testing application forms of all six laboratories for personal clinical history of cancer and age at diagnosis. These data were provided by genetics professionals at the time of testing. If information about clinical history of cancer was not available on the application forms, medical records from the genetics departments were evaluated.

Additional data extracted from the *TP53* DNA testing application forms or medical records from the genetics departments included the requested timing of DNA test results (i.e. *treatment-focused* DNA testing, which is used when decisions about primary breast cancer treatment could be impacted by genetic test results [34], or regular DNA testing), *BRCA* status (i.e. whether *BRCA 1*/*BRCA2* testing was performed, including the results) and family history. Information about the family history was coded into three categories: (1) *'family history suggestive of LFS'*: first-degree relative (FDR) and/or second-degree relative (SDR) with a sarcoma, brain tumour or adrenocortical carcinoma (core LFS cancers); (2) *'family history non-suggestive of LFS'*: no FDR and/or SDR with a sarcoma, brain tumour or adrenocortical carcinoma (based on the family pedigree provided by the genetic professional or the notification 'family history is non-contributory'); (3) '*no information*': no information available about the family history of cancer. For *TP53* mutation carriers, additional information was obtained regarding the histological type of breast cancer and the oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) status. The Medical Research Ethics Committee of the University Medical Center Utrecht concluded that the Medical Research Human Subject Acts (WMO) does not apply.

Mutation analysis

Sanger sequence analysis of all coding exons (2–11) and exon/intron boundaries was performed for *TP53* (NM_000546.5) to identify small nucleotide changes and for the identification of larger rearrangement. Multiplex ligation-dependent probe amplification (MLPA) was undertaken using the SALSA MLPA kit P056 (MRC-Holland, Amsterdam, the Netherlands). Sequence variants were classified into five categories based on the degree of likelihood of pathogenicity: (1) 'benign', (2) 'likely benign', (3) 'uncertain significance', (4) 'likely pathogenic', (5) 'pathogenic' [35]. Classes 3–5 were reported to the genetic professional involved.

Results

In total, 370 women diagnosed with breast cancer before the age of 30 years were tested for *TP53* germline mutations in the Netherlands between 2005 and 2016, of whom 32% (119) had a treatment-focused genetic test. Since 2011, there has been a notably steep increase in the number of women tested (Fig. 1). Characteristics of the patients tested are described in Table 1. Mean age at breast cancer diagnosis was 26 years (range 15–29 years). Information about *BRCA* status was available for 356 patients (96%), of whom 15 were found to carry a *BRCA1* pathogenic mutation and four a *BRCA2* pathogenic mutation. Information about family history was available for 284 patients (77%), of whom the majority had a family history non-suggestive of LFS (255/284; 90%). Five patients had a history of LFS-spectrum cancers in addition to young onset breast cancer.

Mutation prevalence

Of the 370 early-onset breast cancer patients analysed for *TP53* germline mutations, test results were available for 364 women. In six women, DNA analysis could not be performed due to insufficient quality of DNA. In eight women (2.2%), a (likely) pathogenic *TP53* germline sequence variant was identified.

Of these variants, six were definitely pathogenic (c.503A > G, c.524G > A, c.637C > T, c.723delC, c.916C > T, and 376 − ?_(993 + ?)del; del exon5-exon9) and two were likely pathogenic (c.587G > A and c.749C > T). In addition, one woman was tested for a specific *TP53* germline mutation that was already known to exist in her family. The majority of carriers of a (likely) pathogenic *TP53* germline sequence variant (6/8) had been referred for treatment-focused genetic testing. The youngest *TP53* mutation carrier was diagnosed with breast cancer at 19 years of age. Histology reports and information about family history of LFS-related cancer were available for seven carriers of a (likely) pathogenic *TP53* germline mutation. Five breast cancers were identified as HER2 positive and two as triple positive (i.e. ER, PR and HER2 positive). Three carriers of a (likely) pathogenic *TP53* germline sequence variant had a family history suggestive of LFS, and three carriers had developed another LFS-related tumour (2 rhabdomyosarcoma, 1 osteosarcoma) prior to their breast cancer diagnosis.

Discussion

This study was designed to evaluate the diagnostic yield of *TP53* genetic testing in early-onset breast cancer patients. Our findings, the largest such study to date, show a steep increase in the number of *TP53* DNA testing applications since 2011. We assume that this increase is the result of changes in national guidelines and the results of international studies [6, 21, 24, 32]. A family history suggestive of LFS was no longer required for *TP53* genetic testing. Consequently, *TP53* DNA genetic testing is now offered to women with early-onset breast cancer more often than it was previously. However, another possible explanation could be the increase of referrals for treatment-focused genetic counselling and testing.

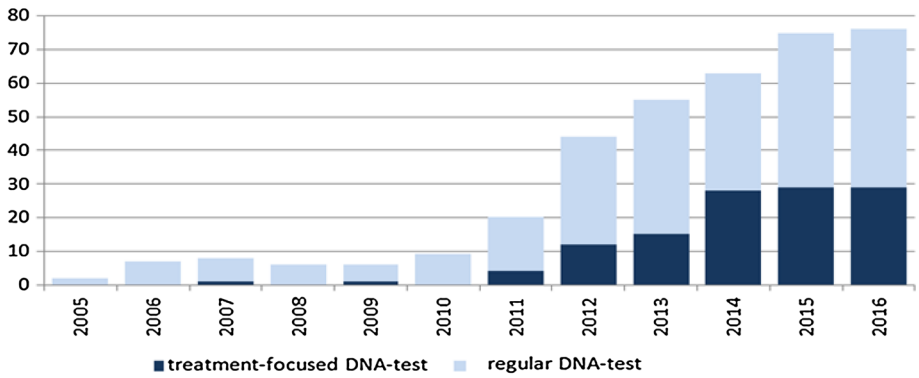

Fig. 1 Number of young breast cancer patients[i] tested for germline *TP53* mutations in the Netherlands 2005–2016

[i] Women diagnosed with invasive breast cancer or carcinoma in situ before the age of 30

Table 1 Clinical characteristics of young breast cancer patients tested for germline *TP53* mutations in the Netherlands 2005–2016

	n (%)
All patients	**370**
Age at diagnosis mean (range)	26 years (15–29 years)
BRCA status	
Negative	326 (88%)
Pathogenic mutation *BRCA1* or *BRCA2*	19 (5%)
VUS *BRCA1* or *BRCA2*	11 (3%)
Unknown	14 (4%)
Family history	
Suggestive of LFS[a]	28 (8%)
Non-suggestive of LFS[b]	256 (69%)
Unknown	86 (23%)
Personal history	
Second LFS-related tumour (other than BC)	5 (1.4%)
Requested time for *TP53* genetic testing	
Treatment-focused testing[c]	119 (32%)
Regular testing	251 (68%)
Carriers of a (likely) pathogenic TP53 sequence variant	**8**
Age at diagnosis mean (range)	25 years (19–28 years)
BRCA status	
Negative	7
Unknown	1
Family history	
Suggestive of LFS[a]	3
Non-suggestive of LFS[b]	4
Unknown	1
Personal history	
Second LFS-related tumour (other than BC)	3
Receptor status breast cancer	
HER2 positive	5
ER, PR and HER2 positive	2
Unknown	1
Request time for *TP53* genetic testing	
Treatment-focused testing[c]	6
Regular testing	2

VUS variant of uncertain significance, *LFS* Li–Fraumeni Syndrome, *BC* breast cancer, *ER* oestrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor 2

[a]First-degree relative and/or second-degree relative with a sarcoma, brain tumour, adrenocortical carcinoma

[b]Not meeting the criteria for family history 'suggestive of LFS'

[c]When decisions about primary breast cancer treatment could be impacted by genetic test results

Our results also show that the *TP53* mutation prevalence among early-onset breast cancer patients was lower than most studies previously reported (Table 2) [9, 11, 22–25]. We found (likely*)* pathogenic *TP53* germline mutations in 2.2% (8/370) of women diagnosed with breast cancer before the age of 30, unselected for family history. To evaluate the clinical utility of 'early-onset breast cancer' as a criterion for identifying *TP53* carriers, it is necessary to investigate the likelihood of a germline *TP53* mutation in young breast cancer patients who did not fulfil other established criteria for *TP53* testing. McCuaig et al. reported the results of *TP53* testing in a very small sample; they found a *TP53* mutation was present in one of 13 (7.7%) cases of breast cancer diagnosed before age 30 who did not meet established criteria for *TP53* testing [24]. More recently, Bougeard et al. reported on a larger series of 333 early-onset breast cancer patients (≤ 30 years) [11]. Patients had been selected for *TP53* genetic testing on the basis of clinical criteria that

Table 2 Results of studies exploring *TP53* germline mutation prevalence among early-onset breast cancer patients

Study	Subjects	N	*BRCA* status	Family history/personal history of multiple LFS-related tumours	TP53 mutation prevalence (%)
Lalloo et al. [22]	Breast cancer < 31[a]	82[b]	Negative	Unselected	4.9% (4/82)
Ginsburg et al. [25]	Breast cancer < 30	95	Negative	Unselected	0% (0/95)
Gonzalez et al. [9]	Breast cancer < 30	14	Negative	No cancer in FDR or SDR	7.1% (1/14)
Mouchawar et al. [23]	Breast cancer < 30[a]	43[b]	Negative	Unselected	4.7% (2/43)
McCuaig et al. [24]	Breast cancer < 30	13[b]	Negative	Did not meet classic LFS, LFL or Chompret 2009 criteria	7.7% (1/13)
Bougeard et al. [11]	Breast cancer < 31	NR[b]	NR	Did not meet Chompret 2009 criteria	6% (NR)
Eccles et al. [26]	HER2 + breast cancer < 31	71[b]	Negative	Unselected	8.5% (5/71)
Bakhuizen et al. [present study]	Breast cancer < 30	233[b,c]	Negative	No sarcoma, brain tumour or ACC in FDR or SDR + no second LFS-related tumour (other than BC)	0.9% (2/233)

FDR first-degree relative, SDR second-degree relative, NR not reported, ACC adrenocortical carcinoma, BC breast cancer

[a]Population based cohort

[b]Subgroup of total study population

[c]256 patients had a family history non-suggestive of LFS (see Table 1), of whom 4 had a second LFS-related tumour, 12 carry a *BRCA* mutation and for 7 women the *BRCA*-status was unknown

corresponded, in most cases, with the Chompret criteria (version 2009). Of these women, 14% were found to have a *TP53* mutation. Among the patients who did not fulfil the 2009 version of the Chompret criteria, the mutation detection rate was 6%. However, the exact number of women who did not fulfil these criteria was not reported. In our cohort, six of eight carriers of a (likely) pathogenic *TP53* mutation did meet other established criteria for *TP53* testing, in addition to 'early-onset breast cancer'. The *TP53* mutation prevalence was 0.9% (2/233) among early onset breast cancer *BRCA1*/*BRCA2* mutation negative patients without additional features indicative of LFS (family history suggestive of LFS and/or a personal history of multiple LFS-related tumours).

Our study highlights the importance of critically reviewing established testing criteria. Women with breast cancer diagnosed before the age of 30 without additional features indicative of LFS can be reassured that they have a very low chance of being a *TP53*-mutation carrier. This raises the question of whether age of onset actually is an appropriate criterion for *TP53* genetic testing.

Several studies have reported the frequency of *TP53* mutations in different cohorts of breast cancer patients [16, 20, 26, 36–39]. For women unselected by family history, with a personal history of breast cancer up to age 36 years of age and who are *BRCA1*/*BRCA2* mutation negative, the proportion of *TP53* germline mutation carriers ranged between 2.3% and 4.2% [16, 36–38]. Sample size varied from 30 to 128. Two studies explored *TP53* genetic testing in patients with HER2-amplified breast cancer, unselected for family history suggestive of LFS [26, 39]. Eccles and colleagues reported a *TP53* mutation prevalence of 3% (9/304) among women diagnosed with HER2+ breast cancer (ER/PR status was not uniform) under the age of 41, and 8.5% (5/71) for women diagnosed before 31 years [26]. In a cohort of women with HER2+ breast cancer diagnosed ≤ 50 years without a known family history, consistent with Chompret criteria, *TP53* mutations were identified in 1/195 (0.5%) [39]. In a review of 37 multigene panel studies (including mainly patients who were referred due to personal or family history of breast cancer), the overall *TP53* mutation prevalence ranged from 0 to 4.4% [20]. For *BRCA1*/*BRCA2* mutation negative patients of European ancestry undergoing breast cancer multigene panel testing (MGPT), the weighted frequency of *TP53* mutation carriers was 0.3%. Although patients were diverse in age of onset and family history, it is noteworthy that approximately half of the *TP53* mutation carriers detected by MGPT did not meet NCCN criteria for LFS testing (e.g. classic LFS criteria or Chompret 2015 criteria) [6]. The findings of these studies suggest that it may be beneficial to consider an expanding age of onset or HER2-positive tumour status for LFS testing criteria. However, larger studies are needed to provide more precise estimates of *TP53* germline mutations in different cohorts of breast cancer patients.

An evaluation of the benefits and concerns raised by offering *TP53* genetic testing is also warranted. The most reported justifications for the utility of *TP53* genetic testing in patients with a low *a priori* probability of carrying a pathogenic *TP53* variant, concerns potential clinical implications [20, 24, 40, 41]. First, there are important consequences for primary breast cancer treatment. If a woman is proven to be a *TP53* mutation carrier, she may opt for bilateral mastectomy to reduce the risk of a second primary

breast cancer. In addition, radiotherapy should be avoided if possible because radiation therapy may increase future cancer risks [42]. Patients without a genetic predisposition can be reassured that their risk of a secondary breast cancer is not substantially increased. There are also important potential implications for family planning and the use of prenatal diagnostics (e.g. pre-implantation genetic testing (PGD)). Lammens and colleagues evaluated the attitudes towards PGD among high risk family members from LFS and Von-Hippel Lindau families [43]. Approximately half of those contemplating a future pregnancy (23/48) would consider the use of PGD. Of note, over a period of 9 years (2009–2017), 12 couples were referred for counselling on PGD for LFS in the Netherlands, of whom 50% (6/12) started with PGD-treatment [44].

In contrast, there are other issues that complicate genetic testing for *TP53* in clinical practice. Although *TP53* mutation carriers may participate in a comprehensive screening protocol [10, 45–47], determining the optimal risk management is complex because of the wide range of cancer predisposition involved [6, 48].This applies especially to *TP53* mutation carriers identified in non-classic LFS-families due to lack of information about actual phenotypic spectrum and cancer risks in these families [18]. The benefits of intensive annual screening programs must be weighed against the possibility of false positive findings that require additional diagnostic procedures [45, 49]. In addition, a few studies have reported that a substantial proportion of the individuals in families with *TP53* mutations exhibit psychological distress [50–52]. Another relevant aspect, which was highlighted by Azzolini and colleagues, concerns patients who willingly decline *TP53* DNA-analysis following genetic counselling [53]. Almost one-fourth (23.4%; 11/47) of patients decided not to undergo *TP53* testing. Also, in newly diagnosed breast cancer patients who needed to define treatment options, 13% (2/23) consented to *BRCA1*/*BRCA2* genetic testing but declined *TP53* analysis.

In one genetic department in the Netherlands, we have kept records about declined testing. Here we find that 40% (16/39) of early-onset breast cancer patients who were offered *TP53* genetic testing declined to be tested, and of these a considerable proportion (28%; 7/25) occurred in a setting of treatment-focused genetic counselling. These findings emphasize the necessity of thorough genetic counselling and confirm the importance of the recommendations we have made previously about the ten information items about LFS that should be discussed during pre-test counselling [33].

There are some limitations to be reported. First, this is not a population-based series of cases, but rather a nationwide clinical testing cohort. Only young breast cancer patients who were referred for genetic counselling and testing and who had chosen *TP53* mutation testing were included. Between 2005 and 2016, 965 women were diagnosed with breast cancer before the age of 30 in the Netherlands [1]. Our findings show that 370 early-onset breast cancer patients were tested for *TP53* germline mutations during this 12-year period. This selection might have increased the likelihood of a suggestive family history or personal history of multiple LFS-related tumours. In that case, the actual *TP53* mutation prevalence among early onset breast-cancer patients may be even lower than we report. Furthermore, the degree to which information about family history was mentioned in the DNA-testing application forms differed. These data were provided by genetics professionals at the time of testing and are based on the patient's own knowledge of their family history. Particularly in the case of treatment-focused testing, family cancer history will not be verified by pathology reports. Therefore, we may have missed information regarding family history. Another issue concerns mosaic *TP53* mutations. High-coverage NGS provides new opportunities to identify germline or somatic mosaicism that was undetectable or nearly undetectable with Sanger sequencing [17]. Since we have performed Sanger sequence analysis, we may have missed mosaic *TP53* mutations. However, as mosaicism in *TP53* is probably very rare [54], additional NGS-results are unlikely to have a large impact on the overall *TP53* mutation prevalence among early-onset breast cancer patients.

In conclusion, for early-onset breast cancer patients without additional features indicative of LFS (i.e. family history suggestive of LFS or a personal history of multiple LFS-related tumours) the probability of finding a germline *TP53* mutation is exceedingly low. This is useful information for genetic counselling. However, since *TP53* mutation prevalence was comparable or even higher in some studies selecting patients with breast cancer at an older age or HER2-positive breast cancers, the question is raised whether very early age of onset is an appropriate LFS testing criterion. Further research is warranted to determine the most appropriate *TP53* testing strategy for women diagnosed with breast cancer. In the interim, a careful approach to genetic counselling for LFS is needed as we have noted that a substantial number of breast cancer patients who were offered *TP53* DNA-analysis following genetic counselling declined to be tested.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The Medical Research Ethical Committee concluded that the Medical Research Human Subject Acts (WMO) does not apply.

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