Original Article

The yield and effectiveness of breast cancer surveillance in women with PTEN Hamartoma Tumor Syndrome

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BACKGROUND: Women with *PTEN* Hamartoma Tumor Syndrome (PHTS) are offered breast cancer (BC) surveillance because of an increased BC lifetime risk. Surveillance guidelines are, however, expert opinion–based because of a lack of data. We aimed to assess the yield and effectiveness of BC surveillance and the prevalence and type of breast disease in women with PHTS. **METHODS:** Sixty-five women with PHTS who visited our center between 2001 and 2021 were included. Surveillance consisted of annual magnetic resonance imaging (MRI) and mammography from ages 25 and 30 years, respectively. **RESULTS:** Thirty-nine women enrolled in the BC surveillance program (median age at first examination, 38 years [range, 24–70]) and underwent 156 surveillance rounds. Surveillance led to detection of BC in 7/39 women (cancer detection rate [CDR], 45/1000 rounds) and benign breast lesions (BBLs) in 11/39 women. Overall sensitivity$_2$ (which excludes prophylactic-mastectomy detected BCs) was 100%, whereas sensitivity$_2$ of mammography and MRI alone was 50% and 100%, respectively. Overall specificity was higher in follow-up rounds (86%) versus first rounds (71%). Regardless of surveillance, 21/65 women developed 35 distinct BCs (median age at first diagnosis, 40 years [range, 24–59]) and 23/65 developed 89 BBLs (median age at first diagnosis, 38 years [range, 15–61]). Surveillance-detected BCs were all T1 and N0, whereas outside surveillance-detected BCs were more often ≥T2 (60%) and N+ (45%) ($p < .005$). **CONCLUSIONS:** The findings show that annual BC surveillance with MRI starting at age 25 years enables detection of early-stage BCs. Performance measures of surveillance and CDR were both high. BBLs were commonly present, underlining the importance of evaluation of all lesions independently. ***Cancer* 2022;128:2883-2891**.

KEYWORDS: breast cancer, breast cancer early diagnosis, breast cancer surveillance in high-risk women, PTEN gene variants, PTEN Hamartoma Tumor Syndrome.

INTRODUCTION

PTEN Hamartoma Tumor Syndrome (PHTS) is an umbrella term describing a spectrum of clinical manifestations caused by pathogenic germline variants in the *PTEN* gene.[1–3] *PTEN* is involved in the pathogenesis of various hereditary cancers, particularly hereditary breast cancer (BC),[4–6] which is the most common malignancy in women with PHTS (lifetime risk, 67%–85%).[7] Moreover, previous studies showed that 67%–75% of women with PHTS develop benign breast lesions (BBLs), though the exact prevalence is still unknown.[5,8,9]

Because of the increased risk of BC, the American Cancer Society included women with PHTS in their expert opinion–based recommendations for BC surveillance with breast magnetic resonance imaging (MRI) scans.[10] Because BC risk estimates for women with PHTS are similar to those reported for women with BRCA1/2 germline variants, women with PHTS currently undergo the same expert opinion–based BC surveillance in many European countries.[11,12] This consists of annual breast MRI from age 25 years onward and supplemental annual mammography from age 30 years onward.[13] Recently, the European Reference Network on Genetic Tumor Risk Syndromes published expert opinion–based guidelines on BC surveillance in women with PHTS, proposing annual MRI from age 30 years onward and supplemental biennial mammography from age 40 years onward, acknowledging the documented low added value of mammography in younger high-risk women, most notably BRCA1/2 carriers.[14,15]

Actual data on BC surveillance in women with PHTS is virtually absent because PHTS is a rare syndrome with an estimated prevalence of 1 in 200,000–250,000.[16] Moreover, available BC risk estimates in women with PHTS are likely overestimated

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DOI: 10.1002/cncr.34326, **Received:** March 22, 2022; **Revised:** May 2, 2022; **Accepted:** May 10, 2022, **Published online** June 1, 2022 in Wiley Online Library (wileyonlinelibrary.com)

because of ascertainment bias.[7,17] Consequently, the effectiveness of current BC surveillance programs is uncertain, emphasizing the need for evaluation.

The primary objective of this study was to evaluate the yield and effectiveness of BC surveillance in women with PHTS. Additionally, our study aimed to assess the prevalence and type of benign and malignant breast disease in women with PHTS, regardless of whether surveillance was initiated.

METHODS

Study setting and design

This single-institution retrospective study was approved by the institutional review board. The need for informed consent was waived. Women (aged ≥18 years) with a confirmed (likely) pathogenic PTEN variant ($n = 62$) or a variant of unknown significance with a clear PHTS phenotype ($n = 3$) who visited the Radboud University Medical Center between January 2001 and February 2021 were included. The Radboud University Medical Center is a national PHTS expert center and 1 of the European PHTS expert centers affiliated with the European Reference Network on Genetic Tumor Risk Syndromes.[18] Patients with a first- or second-degree relative who developed BC were considered to have a family history of BC.

Women with PHTS who started BC surveillance at our institution were monitored within our high-risk surveillance program, in line with the American Cancer Society guidelines[10] and the National PHTS guideline.[11] Annual breast MRI and mammography were performed from the age of 25 and 30 years onward, respectively. After age 60 years, MRI was suspended and only mammography was performed annually or biannually. Mammograms were obtained with a full-field digital mammography machine in 2 standard views (mediolateral-oblique and craniocaudal). MRI protocols varied over time, but always included T1-weighted pre- and postcontrast examinations that met the minimal criteria of the European Society of Breast Imaging.[19] Reporting of breast examinations was performed according to the various editions of the American College of Radiology Breast Imaging–Reporting and Data System (BI-RADS) lexicon.[20]

Reports of surveillance imaging examinations were collected from patients' medical records. For each examination, we assessed the detection of any benign or malignant breast finding. In case of combined reports from MRIs and mammography, lesions were only scored as visible if explicitly mentioned in the report section of that specific modality. BI-RADS scores 0, 3, 4, and 5 were regarded as positive findings and BI-RADS scores 1 and 2 as negative findings. We assessed whether eventual positive findings led to a recall and whether these recalls led to biopsy.

Biopsy results and histopathological characteristics of breast lesions were obtained from the local or the national pathology archive. Parameters included tumor size, histological type, and pathological TNM stage. When pathological TNM was unknown, we recorded the clinical TNM. For BBLs, the histological type was recorded.

Outcome measures

A surveillance round was defined as the yearly examination(s) performed in asymptomatic women. The first round was defined as the first surveillance examination(s). Follow-up rounds were performed between 10 and 24 months after a previous surveillance examination. Calculations were performed for MRI and mammography separately, as well as for the combination. We calculated the recall rate, the biopsy rate, and the cancer detection rate (CDR) as the number of positive findings, number of biopsies performed, and number of BCs detected on a per-patient level per 1000 examinations, respectively. The positive predictive value 1 ($PPV1_{recall}$) was defined as the fraction of recalls that led to BC detection among all women recalled for positive examinations. The positive predictive value 3 ($PPV3_{biopsy}$) was defined as the number of examinations with BC detected among women who received a biopsy. Interval cancers were defined as BCs diagnosed after negative results on surveillance imaging and before the next surveillance examination. Sensitivity and specificity of the surveillance program were calculated on a per-breast level. Overall, sensitivity was defined as the number of surveillance-detected BCs divided by the total number of BCs detected. For $sensitivity_1$, surveillance-detected BCs, interval cancers, and BCs detected at prophylactic mastectomy were considered. For $sensitivity_2$, only surveillance-detected BCs and interval cancers were considered, excluding additional BCs detected at prophylactic mastectomy. Specificity was calculated as the number of assessments that did not lead to recall divided by the total number of surveillance examinations without subsequent BC detection.

Statistical analysis

The overall surveillance performance measures and separate results of the first-round versus follow-up rounds were analyzed using tests for proportions and Fisher exact tests, including 95% CIs.[21] We compared characteristics of surveillance-detected BCs with BCs detected outside surveillance using Kruskal–Wallis rank-sum tests or Fisher exact tests. Descriptive statistics were summarized as measures of frequency or central tendency, and of dispersion or variation. Results were considered statistically

significant with a 2-sided $p < .05$ and analyses were performed using R software version 3.6.1.[22]

RESULTS

Sixty-five women with PHTS visited our expert center (Table 1; Fig. 1). The median age at PHTS diagnosis was 35 years (range, 8–71). In 4 women (6%), the PHTS diagnosis was suggested by the recent BC diagnosis. Moreover, 9 additional women (14%) had a personal history of BC but were not tested for a PTEN variant at the time of BC diagnosis.

Women with PHTS enrolled in the BC surveillance program

Of all 65 women, 39 (60%) enrolled in the BC surveillance program. The median age at first and last surveillance examination was 38 years (range, 24–70) and 40 years (range, 26–72), respectively. Thirty-four (87%) women had multiple examinations with a median follow-up time of 4 years (range, 1–15). The total follow-up time was 135 years. In total, 39 women underwent 264 surveillance examinations during 156 surveillance rounds, consisting of 108 combined MRI and mammography rounds, 26 MRI-only rounds, and 22 mammography-only rounds. Moreover, 12 short-term (i.e., 6-month) follow-up rounds were performed in 10 women because of dubious imaging findings of the breast at the yearly surveillance round, which were not suspicious enough to perform a biopsy. These consisted of 1 combined MRI and mammography, 9 MRI only, and 2 mammography-only examinations.

Overall, surveillance led to 34 recalls in 18 women. Nine women were recalled more than once: 4 women were recalled twice, 3 women 3 times, and 2 women 4 times. Recalls were based on mammography in 6 cases, on MRI in 10 cases, and on both modalities in 18 cases. The overall recall rate was 20%. Recalls led to 18 image-guided biopsy in 14 women. Of these, 3 were induced by mammography, 11 by MRI, and 4 by both modalities. Biopsies were performed using ultrasound guidance in 11 cases, stereotactic guidance in 2 cases, and MRI guidance in 5 cases. The biopsy rate was 12%.

Surveillance led to BC detection in 7 breasts within 7 women (median age at first diagnosis, 43 years [range, 31–55]). One woman was diagnosed by mammography and 1 by MRI when only 1 modality was available, 3 women by MRI only when both imaging modalities were available, and 2 women by both imaging modalities. The CDR was 45/1000 rounds (95% CI, 20–94 rounds). After excluding women with a personal history of BC or women with either a personal or family history of BC, the CDR was 43/1000 rounds (95% CI, 17–94 rounds) and 20/1000 rounds (95% CI, 4–78 rounds), respectively, which were both not statistically different from the overall CDR ($p = 1.00$). $PPV1_{recall}$ was 0.21 and $PPV3_{biopsy}$ was 0.39.

Within the 7 affected breasts, 10 distinct BCs were found: 8 BCs after performing a biopsy in 7 breasts and 2 BCs at pathology after mastectomy in 2 affected breasts. Two BCs were ductal carcinoma *in situ* (DCIS) and 8 were invasive (Table 3). Six of the 7 (86%) women diagnosed with surveillance-detected BC had also been diagnosed with pathology-confirmed BBLs: 4 after biopsy induced by surveillance, 1 after prophylactic mastectomy, and 1 after biopsy outside of surveillance. Regardless of

TABLE 1. Characteristics of all 65 Women with *PTEN* Hamartoma Tumor Syndrome

Characteristics	Overall ($N = 65$)	Women with PHTS enrolled in the BC surveillance program	
		Yes ($n = 39$)	No ($n = 26$)
Index patient[a], *n/N* (%)	34/65 (52%)	16/39 (41%)	18/26 (69%)
Age at PHTS diagnosis, median (range)	35 (8–71)	37 (20–70)	20 (8–71)
Age at last clinical follow-up, median (range)	40 (18–73)	41 (26–73)	26 (18–71)
Years of clinical follow-up after PHTS diagnosis, median (range)	4 (0–17)	5 (0–17)	2 (0–17)
Personal history of BC, *n/N* (%)	13/65 (20%)	4/39 (10%)	9/26 (35%)
Family history of BC[b], *n/N* (%)	14/65 (22%)	11/39 (28%)	3/26 (12%)
Personal or family history of BC, *n/N* (%)	23/65 (35%)	13/39 (33%)	10/26 (38%)
Family history of PHTS, *n/N* (%)	36/65 (55%)	26/39 (67%)	10/26 (38%)
No breast findings, *n/N* (%)	32/65 (49%)	19/39 (49%)	13/26 (50%)
BBLs without BC detection[b], *n/N* (%)	12/65 (18%)	9/39 (23%)	3/26 (12%)
BBLs[c], *n/N* (%)	23/65 (35%)	18/39 (46%)	5/26 (19%)
BC[c], *n/N* (%)	21/65 (32%)	11/39 (28%)	10/26 (38%)

Abbreviations: BBLs, benign breast lesions; BC, breast cancer; PHTS, *PTEN* Hamartoma Tumor Syndrome.
[a] The first patient diagnosed with PHTS in a family because of clinical signs.
[b] Patients with a first- or second-degree relative who developed BC.
[c] Pathology-confirmed findings.

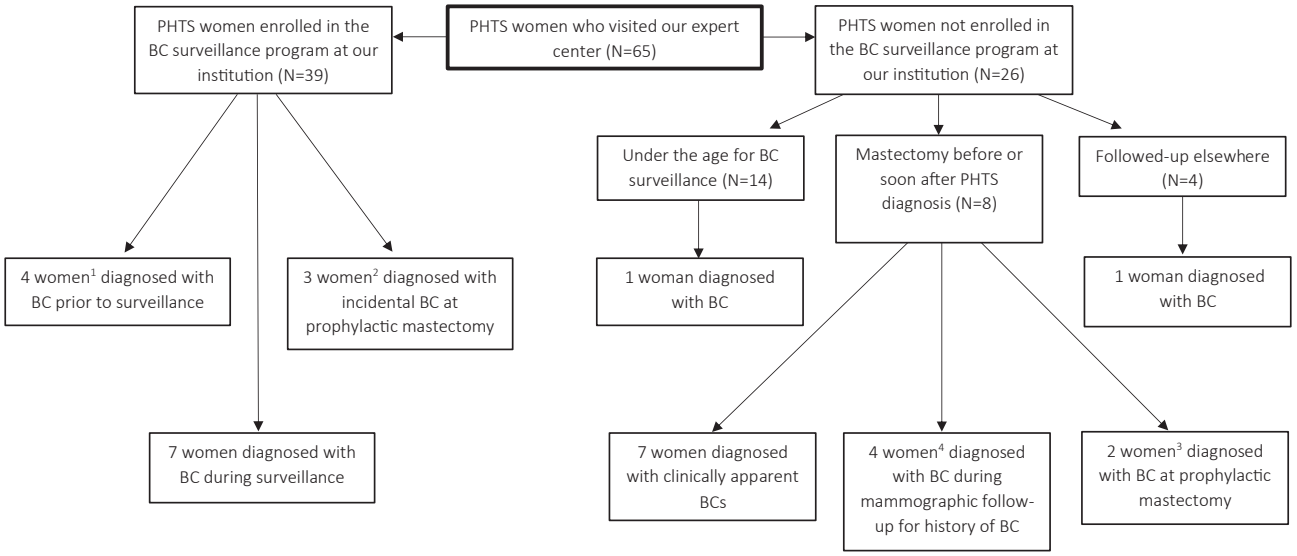

Figure 1. Flowchart of women with PHTS included in the study. Abbreviations: BC, indicates breast cancer; PHTS, *PTEN* Hamartoma Tumor Syndrome.[1] One woman was diagnosed with BC both before and during surveillance.[2] Two women were also diagnosed with BC by means of surveillance.[3] One woman was also diagnosed with BC before PHTS diagnosis.[4] All 4 women had a history of BC.

BC detection, surveillance-induced biopsies resulted in detection of BBLs in 11 women.

No interval cancers were detected. Twelve women underwent prophylactic mastectomy during surveillance or soon after the last examination, resulting in 4 incidental BCs in 4 breasts within 3 women that were not previously identified during surveillance. Two of these 3 women were diagnosed with surveillance-detected BC in 1 breast and then opted for prophylactic mastectomy of the contralateral breast, yielding 1 DCIS and 1 invasive BC (Fig. 2). The remaining woman was diagnosed with bilateral DCIS after bilateral prophylactic mastectomy. Prophylactic mastectomy yielded pathology-confirmed BBLs in 10 women. The overall surveillance program had a sensitivity$_1$ of 64%, a sensitivity$_2$ of 100%, and a specificity of 82% (Table 2).

Women with PHTS not enrolled in the BC surveillance program

In total, 26 women did not enroll in the BC surveillance program of our institution (Fig. 1). In this subgroup, a total of 17 distinct BCs were diagnosed within 10 women. Nine BCs were symptomatic, 3 were detected at prophylactic mastectomy, and 5 during mammographic follow-up in women with history of BC.

Fourteen of these 26 women were underage for surveillance at the last clinical follow-up (n = 12) or opted for prophylactic mastectomy before the age of 25 (n = 2). Among these 14 women, 1 developed BC at the age of 24 and consequently underwent PTEN testing. In 3 other women, 14 imaging examinations (13 MRIs and 1 mammography) were performed for clinical complaints (i.e., lumps and/or pain). Of these 3 women, 2 were diagnosed with BBLs at imaging (i.e., no biopsy) and the other woman was diagnosed with fibroadenomas after biopsy.

The remaining 12 of 26 women (median age at last clinical follow-up, 51 years [range, 29–71]) were not enrolled in the BC surveillance program at our institution either because of BC and subsequent mastectomy before or soon after PHTS diagnosis (n = 8) or because of BC surveillance performed outside our institution (n = 4). Of the 4 women followed up elsewhere, clinical information regarding BC surveillance was available for 3 women; however, data on the surveillance strategy or mode of BC detection were missing. The remaining woman was under mammographic follow-up for prior history of BC diagnosis, detected at age 48 years.

Pathology of BBLs and BCs

In total, 23 of 65 (35%) women were diagnosed with 89 distinct BBLs (median age at first diagnosis, 38 years [range, 15–61]), either at diagnostic biopsy or prophylactic mastectomy (Fig. 3). Of all 39 women who started BC surveillance, 18 (46%) were diagnosed with BBLs, either outside or during surveillance.

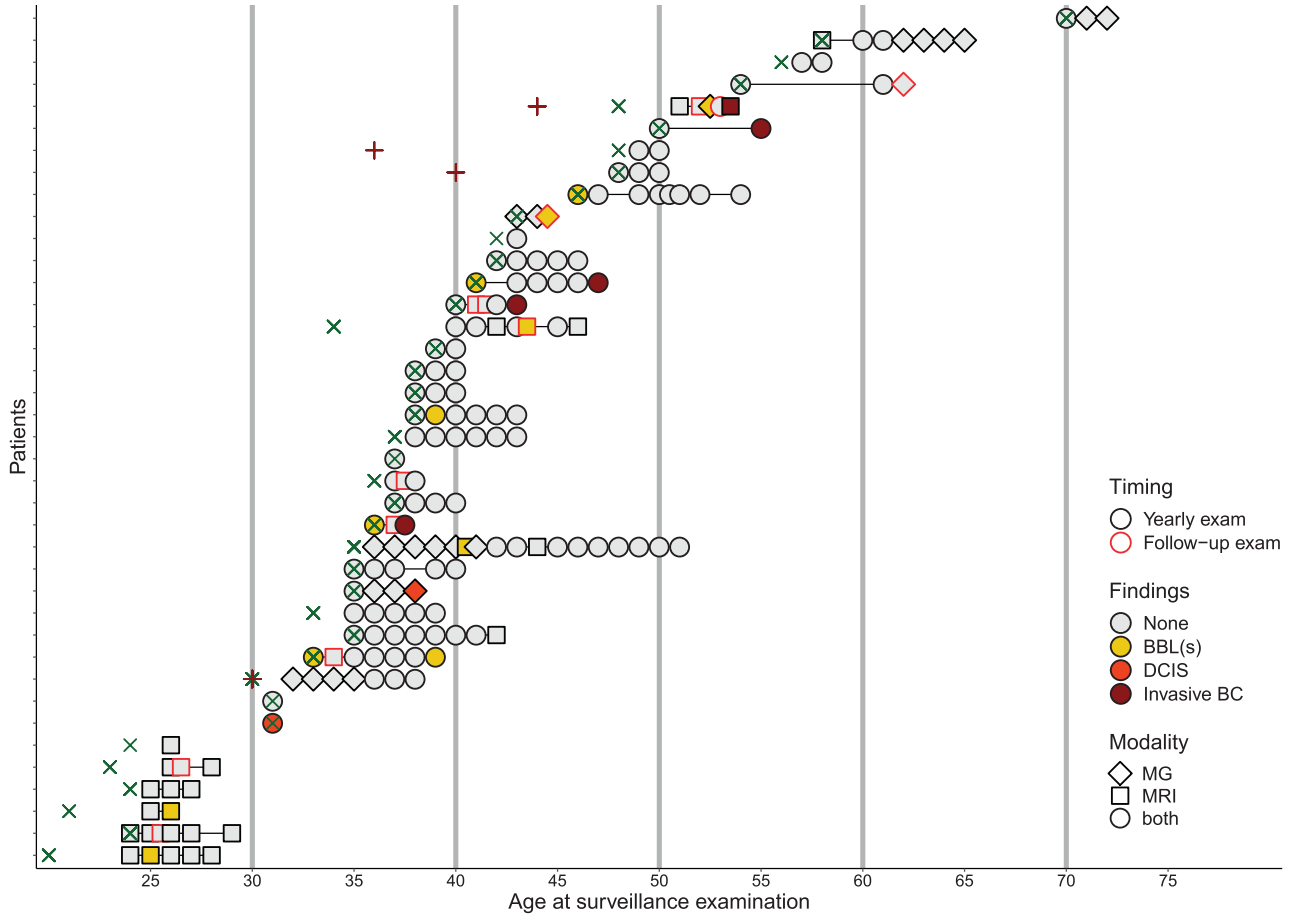

Figure 2. Timeline of BC surveillance. Each horizontal line represents 1 unique woman. Each circle, square, or diamond represents 1BC surveillance examination. A green cross represents the age at PHTS diagnosis. A red plus represents the age of BC detection before the start of surveillance. BCs found at prophylactic mastectomy are not depicted. All findings concern pathology-confirmed breast lesions. Abbreviations: BBL indicates benign breast lesion; DCIS, ductal carcinoma *in situ*; MG, mammography; MRI, magnetic resonance imaging; PHTS, *PTEN* Hamartoma Tumor Syndrome.

Twenty-one of 65 (32%) women were diagnosed with 35 distinct BCs (median age at first diagnosis, 40 years [range, 24–59]). Of the 21 women diagnosed with BC, 12 (57%) were also diagnosed with BBLs. Based on the context of detection, we identified 4 groups: BCs detected after positive findings during BC surveillance ($n = 10$), BCs detected outside surveillance ($n = 13$), BCs detected during mammographic follow-up for history of BC ($n = 5$), and BCs detected at prophylactic mastectomy ($n = 7$) (Table 3). Invasive BCs found outside surveillance had a higher tumor stage compared with BCs found during surveillance and BCs found at prophylactic mastectomy ($p = .002$). Furthermore, BCs found outside surveillance were more often lymph node–positive than BCs detected during surveillance ($p = .002$).

DISCUSSION

To our knowledge, the present study is unique because it represents the first comprehensive overview of the yield and effectiveness of a well-organized BC surveillance program in a relatively large cohort of women with PHTS, acknowledging that PHTS is rare. Despite the high recall and biopsy rates observed in our study, particularly in the first round, the PPVs for recall and biopsy compare favorably with those reported for other women at high risk of BC undergoing surveillance,[23–27] indicating that BC surveillance in women with PHTS can be considered effective.

The overall cancer yield in our study was particularly high (CDR, 45 per 1000 rounds; 95% CI, 20–94 rounds), and remained high when excluding patients with

TABLE 2. Performance Measures of (combined) MRI and Mammography Surveillance Examinations in Women with *PTEN* Hamartoma Tumor Syndrome Enrolled in the BC Surveillance Program

Parameter	Overall	First round	Follow-up rounds	*p*
Surveillance rounds, No.[a]	156	39	117	-
Recall rate	202.4 (146.0–272.7) [34/168]	307.7 (175.5–477.3) [12/39]	170.5 (112.2–249.0) [22/129]	.10
Biopsy rate	115.4 (71.7–178.7) [18/156]	128.2 (48.2–282.3) [5/39]	111.1 (62.9–185.9) [13/117])	.78
$PPV1_{recall}$	0.21 (0.09–0.38) [7/34]	0.08 (0.00–0.40) [1/12]	0.27 (0.12–0.50) [6/22]	.38
$PPV3_{biopsy}$	0.39 (0.18–0.64) [7/18]	0.2 (0.01–0.70) [1/5]	0.46 (0.20–0.74) [6/13]	.60
CDR	44.9 (19.8–93.8) [7/156]	25.6 (1.3–150.8) [1/39]	51.3 (21.0–112.9) [6/117]	.68
CDR excluding women with a personal history of BC	42.6 (17.4–94.3) [6/141]	28.6 (1.5–166.2) [1/35]	47.2 (17.5–111.9) [5/106]	1.00
CDR excluding women with either a personal or family history of BC[b]	20.2 (3.5–78.1) [2/99]	0 (0–160.2) [0/26]	27.4 (4.8–104.4) [2/73]	1.00
$Sensitivity_1$	63.6 (31.6–87.6) [7/11]	100 (5.5–100) [1/1]	60.0 (27.4–86.3) [6/10]	1.00
$Sensitivity_2$	100 (56.1–100) [7/7]	100 (5.5–100) [1/1]	100 (51.7–100) [6/6]	1.00
Specificity	81.9 (74.6–87.5) [122/149]	71.1 (53.9–84.0) [27/38]	85.6 (77.3–91.3) [95/111]	.08
MRI examinations, No.	134	36	98	–
Recall rate	180.6 (123.4–255.2) [26/144]	277.8 (147.9–454.3) [10/36]	148.1 (89.6–232.4) [16/108]	.13
Biopsy rate	119.4 (66.1–180.8) [16/134]	138.9 (52.3–302.9) [5/36]	102.0 (52.7–183.8) [11/98]	.90
$PPV1_{recall}$	0.23 (0.10–0.44) [6/26]	0.10 (0.01–0.46) [1/10]	0.31 (0.12–0.59) [5/16]	.35
$PPV3_{biopsy}$	0.38 (0.16–0.64) [6/16]	0.2 (0.01–0.70) [1/5]	0.45 (0.18–0.75) [5/11]	.67
CDR	44.8 (18.3–99.1) [6/134]	27.8 (1.5–162.0) [1/36]	51.0 (18.9–120.6) [5/98]	1.00
CDR excluding women with a personal history of BC	40.7 (15.1–97.0) [5/123]	30.3 (1.6–175.1) [1/33]	44.4 (14.3–116.2) [4/90]	1.00
CDR excluding women with either a personal or family history of BC[b]	22 (3.8–84.7) [2/91]	0 (0–165.8) [0/25]	30.3 (5.3–114.8) [2/66]	1.00
$Sensitivity_1$	85.7 (42.0–99.2) [6/7]	100 (5.5–100) [1/1]	83.3 (36.5–99.1) [5/6]	1.00
$Sensitivity_2$	100 (51.7–100) [6/6]	100 (5.5–100) [1/1]	100 (46.3–100) [5/5]	1.00
Specificity	84.4 (76.7–90.0) [108/128]	74.3 (56.4–86.9) [26/35]	88.2 (79.4–93.7) [82/93]	.06
Mammography examinations, No.	130	31	99	–
Recall rate	82.7 (44.1–146.6) [11/133]	64.5 (11.3–228.4) [2/31]	88.2 (43.7–165.2) [9/102]	1.00
Biopsy rate	53.8 (23.8–111.9) [7/130]	0.0 (0.0–137.3) [0/31]	70.7 (31.3–145.1) [7/99]	.29
$PPV1_{recall}$	0.27 (0.07–0.61) [3/11]	0.0 (0.0–0.80) [0/2]	0.33 (0.09–0.69) [3/9]	1.00
$PPV3_{biopsy}$	0.43 (0.12–0.80) [3/7]	0.0 (0.0–0.0) [0/0]	0.43 (0.12–0.80) [3/7]	1.00
CDR	23.1 (6.0–71.1) [3/130]	0.0 (0.0–137.3) [0/31]	30.3 (7.9–92.4) [3/99]	1.00
CDR excluding women with a personal history of BC	25.9 (6.7–79.4) [3/116]	0 (0.0–150.2) [0/28]	34.1 (8.8–103.4) [3/88]	1.00
CDR excluding women with either a personal or family history of BC[b]	12.5 (0.7–77.3) [1/80]	0 (0.0–200.5) [0/20]	16.7 (0.9–101.4) [1/60]	1.00
$Sensitivity_1$	30.0 (8.1–64.6) [3/10]	0.0 (0.0–94.5) [0/1]	33.3 (9.0–69.1) [3/9]	1.00
$Sensitivity_2$	50.0 (18.8–81.2) [3/6]	0.0 (0.0–94.5) [0/1]	60.0 (17.0–92.7) [3/5]	1.00
Specificity	92.2 (85.8–96.0) [119/129]	93.5 (77.2–98.9) [29/31]	93.8 [86.4–97.4) [90/96]	1.00

Note: Data in parentheses represent 95% CIs; data in brackets represent numerator/denominator.

Abbreviations: BC, breast cancer; CDR, cancer detection rate, $PPV1_{recall}$, positive predictive value of recall, $PPV3_{biopsy}$, positive predictive value of biopsy; $sensitivity_1$, sensitivity including all cancers; $sensitivity_2$, sensitivity excluding cancers detected at prophylactic mastectomies as false-negative findings; specificity, includes cancers detected at prophylactic mastectomy as false-negative findings.

[a] The complete regimen consisted of a combination of magnetic resonance imaging and mammography, when available.

[b] Patients with a first- or second-degree relative who developed BC.

a personal or family history of BC. Our results are on the upper limit of findings reported in BRCA1/2 carriers and other high-risk populations (CDR, 14–44 per 1000 rounds),[23–27] suggesting that the benefits of BC surveillance in women with PHTS are at least comparable to those in other high-risk populations.

Our recall rate (20%) and biopsy rate (12%) were somewhat higher than previously observed in women with other indications for high-risk screening,[25] yet were in line with findings reported by Chiarelli et al. (22% and 7%, respectively).[23] Nonetheless, recall and biopsy rates both dropped during follow-up rounds, whereas $PPV1_{recall}$ and $PPV3_{biopsy}$ increased. These findings confirm once more that comparing prior images with the current ones improves image assessment, which in turn stresses the importance of awareness and early recognition of PHTS to start cancer surveillance timely before any BC has occurred.[28]

Despite the excellent $sensitivity_2$ (excluding BCs detected at prophylactic mastectomy) (100%), the individual $sensitivity_2$ of MRI (100%) and mammography (50%)

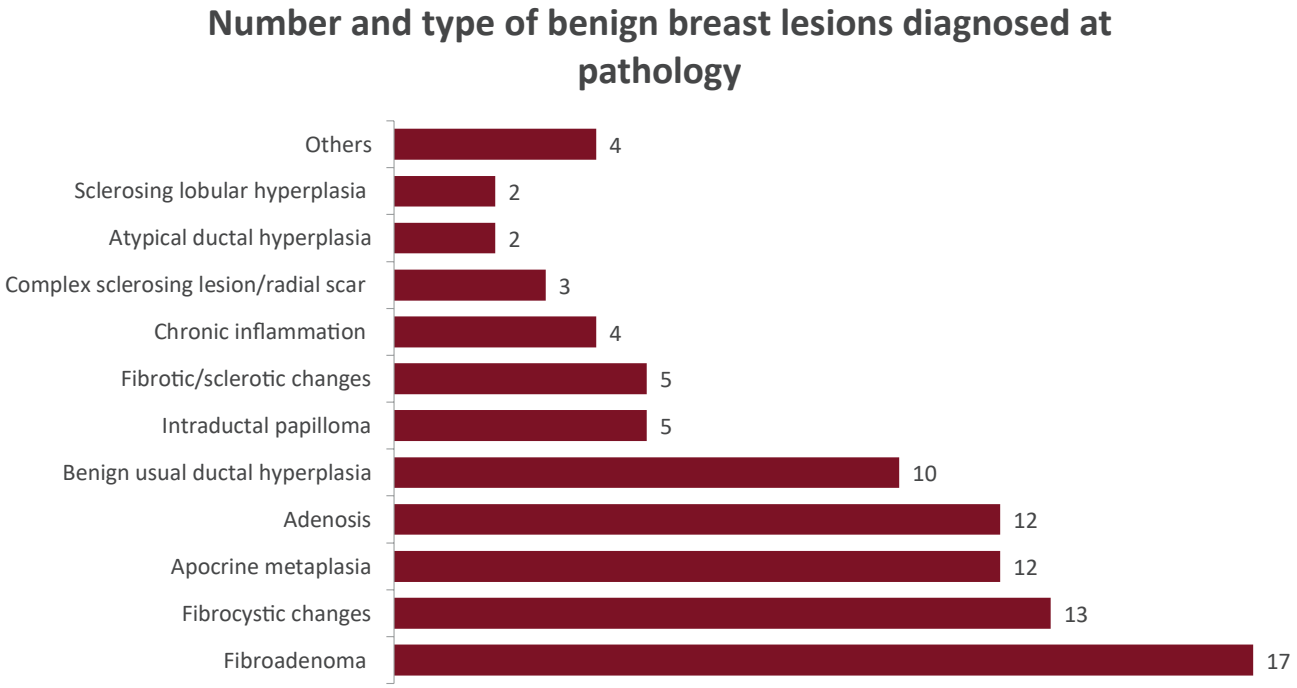

Figure 3. Histologic classification of benign breast lesions in all 23 women with PHTS. Abbreviation: PHTS indicates *PTEN* Hamartoma Tumor Syndrome.

TABLE 3. Characteristics of Breast Cancers Detected in Women with *PTEN* Hamartoma Tumor Syndrome and Age at Detection

Characteristics	Context of BC detection				
	During surveillance[a] (*N* = 10)	Outside BC surveillance[a] (*N* = 13)	During yearly mammographic follow-up[a,b] (*N* = 5)	At prophylactic mastectomy[a] (*N* = 7)	*p*[c]
Median age at detection, (range)	41 (31–55)	40 (24–59)	44 (38–60)	44 [33–60)	.77
Median pathologic size, mm (range)[d]	20 [2–50)	28 [3–65)	9 [4–90)	30 [10–41)	.74
Breast cancers					.001[e]
In situ disease, *n/N* (%)	2/10 (20%)	2/13 (15%)	5/5 (100%)	6/7 (86%)	
Invasive disease, *n/N* (%)	8/10 (80%)	11/13 (85%)	0/5 (0%)	1/7 (14%)	
Histologic type of invasive BCs					.61
Invasive carcinoma of no special type NOS (ductal carcinoma), *n/N* (%)	6/8 (75%)	10/11 (91%)	0/0 (0%)	1/1 (100%)	
Other, *n/N* (%)	2/8 (25%)	1/11 (9%)	0/0 (0%)	0/1 (0%)	
T stage[f]					.002[e]
pT1, *n/N* (%)	6/6 (100%)	4/10 (40%)	0/0 (0%)	1/1 (100%)	
$p \geq$T2, *n/N* (%)	0/6 (0%)	6/10 (60%)	0/0 (0%)	0/1 (0%)	
N stage					.002[e]
pN–, *n/N* (%)	8/8 (100%)	5/11 (55%)	0/0 (0%)	0/0 (0%)	
pN+, *n/N* (%)	0/8 (0%)	6/11 (45%)	0/0 (0%)	0/0 (0%)	
M stage					>.9
M0, *n/N* (%)	8/8 (100%)	9/10 (90%)	0/0 (0%)	1/1 (100%)	
M1, *n/N* (%)	0/8 (0%)	1/10 (10%)	0/0 (0%)	0/1 (0%)	

Abbreviation: BC, breast cancer.
[a]Median (range) or frequency (%).
[b]Cancers detected during yearly mammographic surveillance in women followed up for history of BC.
[c]Kruskal–Wallis rank sum test; Fisher exact test.
[d]Pathologic tumor size is known for 8 BCs detected during BC surveillance, for 10 BCs detected outside BC surveillance, for 3 BCs detected during mammographic follow-up, and for 4 BCs detected at prophylactic mastectomy.
[e]Statistically significant.
[f]T stage is known for 6 of 8 invasive BCs detected during BC surveillance, for 10 of 11 invasive BCs detected outside BC surveillance, and for 1 of 1 invasive BC detected at prophylactic mastectomy.

differed noticeably, thereby confirming the poor performance of mammography as previously reported in women at high hereditary risk (e.g., BRCA1/2 carriers [MRI, 71%–96%; mammography, 19%–51%]).[23–25] The overall specificity was moderate (82%), but increased in follow-up rounds (86%) versus first rounds (71%). The individual specificity of mammography (92%) and MRI (84%) were both adequate, though 3 of 5 surveillance-detected BCs with both imaging modalities available were visible on MRI only. This strengthens the ideas that the added value of mammography in high-risk women is debatable and that MRI as sole imaging modality might suffice.[27,29]

In line with the results of Warner et al., demonstrating that annual breast MRI in BRCA1/2 carriers contributes to the detection of earlier stage BCs,[30] surveillance-detected BCs were smaller and all lymph node–negative compared with clinically apparent BCs. Likewise, Saadatmand et al. showed that MRI surveillance reduces tumor size and the frequency of lymph-node metastasis in women at increased familial risk of BC.[31] Veenhuizen et al. showed similar results in women with extremely dense breasts without other risk factors.[32] A decreased tumor stage is, particularly in women at high hereditary risk, regarded as a proxy for improved BC-specific survival, thereby confirming once again the effectiveness of BC surveillance in women with PHTS.

In our study, the prevalence of pathology-confirmed BBLs in women with PHTS enrolled in the BC surveillance program (46%) was at the high end of that reported for the general population (30%–60%),[33,34] though somewhat lower than previously reported for patients with PHTS.[5,8] However, the increasing PPVs in follow-up rounds likely imply underreporting of the presence of BBLs, whereas the high prevalence of BBLs in women who also developed BC (86%) might suggest that BBLs are more accurately reported in women who receive a simultaneous diagnosis of BC. Hence, special attention for the differentiation of BBLs from BC is still important for women with PHTS.

Because none of the surveillance-detected BCs were lymph node positive and that 5 of 7 women who developed BC had a negative examination 1 year before BC detection, the annual interval for BC surveillance seems adequate. Moreover, considering that the youngest age at BC diagnosis in our study and reported in literature were 24 and 21 years,[7] respectively, the starting age of 25 years for BC surveillance appears appropriate.

Although our study is unique, limitations still remain. First, because of the limited number of women included, we were unable to evaluate potential variations in the yield and effectiveness of surveillance over time from evolving imaging protocols or patient characteristics such as age and prior BC history. Second, radiologists of our expert center had more experience with women with PHTS than average radiologists, which might have had positive effects on the reported performance measures. Nonetheless, concentrating surveillance in expert centers is desirable to maximize surveillance performance outcomes. Third, despite assessing MRI and mammography reports independently, most examinations were evaluated simultaneously by the same radiologist, thereby possibly affecting the performance of the other modality. Fourth, 2 women with surveillance-detected BC continued BC surveillance elsewhere after starting surveillance at our institution but were referred back to our institution after BC detection. Last, the proportion of women with PHTS that develop BC might be overestimated because our study is likely affected by selection bias. Approximately 35% of the 65 women included in the study had a personal or family history of BC and might represent a higher risk subgroup of the overall adult PHTS population. As shown, the CDR in women without a personal or family history of BC is slightly lower (20 per 1000 rounds), which could not be explained by differences in age, and is likely more generalizable to the entire PHTS population. Nonetheless, the CDR remained high and similar to BRCA1/2 carriers, albeit CIs are wide.

In conclusion, the CDR and performance measures of BC surveillance in women with PHTS were excellent and in line with BRCA1/2 mutation carriers. BC surveillance leads to decreased tumor stage, which is regarded as a proxy for improved BC-specific survival. BBLs were commonly present, implying that evaluation of all lesions independently is important. Overall, this study supports offering annual BC surveillance with breast MRI to women with PHTS from age 25 years onward.

AUTHOR CONTRIBUTIONS

Alma Hoxhaj: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, validation, visualization, writing – original draft, and writing – review and editing. **Meggie M.C.M. Drissen:** Data curation, formal analysis, investigation, methodology, software, validation, visualization, and writing – review and editing. **Janet R. Voss:** Conceptualization, methodology, resources, supervision, visualization, and writing – review and editing. **Peter Bult:** Resources, supervision, and writing – review and editing. **Ritse M. Mann:** Conceptualization, funding acquisition, methodology, resources, supervision, and writing – review and editing. **Nicoline Hoogerbrugge:** Conceptualization, methodology, resources, supervision, and writing – review and editing.

ACKNOWLEDGMENTS

This work was supported by a grant of the Talent Program VIDI for Health Research and Development financed by the Dutch Research Council (NWO) and assigned to Ritse M. Mann (grant no. 016.196.338). The funders had no role in the design or conduct of the study; in the collection, management, analysis, or interpretation of the data; in the preparation,

review, or approval of the manuscript; or in the decision to submit the manuscript for publication.

CONFLICTS OF INTEREST

All authors declare no support from any organization for the submitted work. Ritse M. Mann reports personal fees outside the submitted work from Bayer Healthcare, Siemens Healthineers, BD, and Transonic Imaging for consultancies, and grants/grants pending from Siemens Healthineers, Medtronic, Bayer Healthcare, BD, Screenpoint Medical, Seno Medical, and Koning. There are no other relationships or activities that could appear to have influenced the submitted work.

FUNDING INFORMATION

This work was supported by a grant of the Talent Program VIDI for Health Research and Development financed by the Dutch Research Council (NWO) and assigned to R.M. Mann (grant no. 016.196.338).

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