Genetics in Medicine (2025) 27, 101467

ELSEVIER

Genetics in Medicine
An Official Journal of the ACMG

www.journals.elsevier.com/genetics-in-medicine

BRIEF REPORT

The risk of a second primary cancer in PTEN Hamartoma Tumor Syndrome (PHTS)

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ARTICLE INFO

Article history:
Received 12 August 2024
Received in revised form
16 May 2025
Accepted 19 May 2025
Available online 24 May 2025

Keywords:
hereditary cancer
PTEN
PTEN Hamartoma Tumor Syndrome
second primary cancer risk

ABSTRACT

Purpose: Patients with PTEN Hamartoma Tumor Syndrome (PHTS) have high hereditary cancer risks for breast, endometrial, and thyroid cancer. Patients develop multiple primary cancers, but these risks remain uncertain. We aimed to provide the second primary cancer risk.
Methods: This European cohort study assessed second primary cancer risks with Kaplan-Meier analyses using data from medical files, registries and/or patient questionnaires.
Results: Overall, 279 adult PHTS patients with (a history of) cancer were included (80% female). Among females, 106 (54%) developed a PHTS-related second primary cancer after a PHTS-related first primary cancer, whereas 10 (29%) males developed a PHTS-related second primary cancer after a PHTS-related first primary cancer. The 5- and 10-year PHTS-related second primary cancer risks were 24.5% (95% CI = 18.1-32.5) and 45.7% (95% CI = 36.9-55.4) in females and 14.5% (95% CI = 5.7-34.1) and 19.8% (95% CI = 8.6-41.9) in males, respectively. Furthermore, 5- and 10-year risks for a second primary breast cancer after a first primary breast cancer were 23.3% (95% CI = 14.9-35.2) and 45.6% (95% CI = 33.0-60.2) in females, respectively.

The Article Publishing Charge (APC) for this article was paid by Radboud university/Radboud university medical center.
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doi: https://doi.org/10.1016/j.gim.2025.101467

Conclusion: This study demonstrated that PHTS patients have high second primary cancer risks, which is driven by breast cancer in females. Hence, identifying patients with PHTS before or at first primary cancer diagnosis is essential to enable potential early detection or prevention of a second primary cancer through surveillance or risk-reducing surgery.

Introduction

PTEN Hamartoma Tumor Syndrome (PHTS) is caused by pathogenic germline variants in the tumor suppressor gene *PTEN*. Patient recognition has been a persistent challenge; hence, the estimated prevalence of 1:200,000 is anticipated to be higher.[1,2] Patients have high cancer risks, especially for female breast cancer (BC) with risks up to 76% at the age of 60 years. Endometrial cancer and thyroid cancer (TC) risks are also high with risks up to 22% and 21%, respectively. Colorectal cancer, renal cancer, and melanoma risks are each lower than 10%.[3]

Although reports indicated that patients with PHTS frequently develop multiple primary cancers, there are few estimates of the risk of a second primary cancer.[3-5] A small study reported elevated risks up to 29% for second primary BC 10 years after the first primary BC.[4]

It is reported that the risks of female first primary BC presumably depend on the type of variant, specifically its effect on the coding sequence (coding effect, eg, truncating) and domain location of their *PTEN* germline variant.[3] However, this remains unknown for second primary cancer.

Understanding the second primary cancer risk in PHTS is essential to improve cancer surveillance programs and empower evidence-based decision making regarding surgery. Therefore, the second primary cancer risk in patients with PHTS was assessed in a large European cohort.

Materials and Methods

Patients and clinical information

Adult PHTS patients with (a history of) cancer were recruited retrospectively via genetic centers, PHTS expert centers, and self-recruitment in Europe (Supplemental Methods). Patients were included with a (likely) pathogenic *PTEN* germline variant ($n = 274$), a *PTEN* germline variant of unknown significance and meeting the National Comprehensive Cancer Network genetic testing criteria ($n = 3$),[6] or no genetic test with an obligate carrier status of a *PTEN* germline variant ($n = 2$).

Data collection from medical files, pathology registries, and/or patient questionnaires was as previously described.[3] For Dutch patients ($n = 100$), data to supplement details of cancer diagnoses were collected from the The Netherlands Cancer Registry. The last follow-up was defined as last clinical follow-up, questionnaire completion, or last pathology report, whichever came last.

This study was approved by the institutional ethics committees and written informed consent was obtained when required.

Statistical analyses

Descriptive statistics were performed using appropriate measures according to data distribution. Second primary cancer risk was calculated using Kaplan-Meier analyses, and right-censoring was applied at site-relevant surgery (bilateral mastectomy for BC-specific analyses), last follow-up, or death, whichever came first. PHTS-related cancers included BC (including in situ), endometrial cancer, TC, colorectal cancer, renal cancer, and melanoma. "Any cancer" also included non-PHTS-related cancers. For PHTS-related cancer and BC-specific analyses, patients with a PHTS-related cancer or BC as first primary cancer were included, respectively. The second primary cancer was PHTS-related or BC, respectively. When the first primary cancer and second primary cancer were diagnosed simultaneously, patients were excluded from Kaplan-Meier analyses.

Relative risks for second primary BC after first primary BC in females for *PTEN* coding effect and domain were assessed using multivariable Cox regression (Supplemental Tables 1 and 2). The variables included the type of coding effect (missense or truncating) and domain location (phosphatase, C2, or other domain). Missense was the reference category for coding effect and the C2 domain was the reference category for domain. The proportionality assumption was verified by assessing log-minus-log plots and Schoenfeld residuals.

Analyses were stratified by sex and by first primary cancer timing respective to PHTS diagnosis to address ascertainment bias from cancer patients. Analyses were performed using RStudio (V.4.1.1).

Results

Patient and cancer description

Of 279 included PHTS patients with (a history) of cancer, 80% were female (Table 1). The median age at PHTS diagnosis was 45 years (interquartile range [IQR] = 34-53)

Table 1 Cohort baseline characteristics

Characteristics	Females	Males
Population, *n* (% of total)[a]	224 (80)	55 (20)
Index, *n* (%)[b]	154 (69)	32 (58)
Age at last follow-up, *n* (%)[c]	223 (100)	54 (98)
Age, median (IQR)[d]	51 (40-60)	56 (46-64)
Follow-up after first primary cancer, *n* (%)[c]	222 (99)	54 (98)
Years, median (IQR)	5 (1-11)	5 (1-12)
Age at genetic diagnosis of PHTS, *n* (%)[c]	221 (99)	53 (96)
Age, median (IQR)	45 (34-53)	46 (36-56)
PHTS-related cancer diagnosis, *n* (%)	208 (93)	37 (67)
Age first diagnosis, *n* (%)[c]	207 (100)	37 (100)
Age first diagnosis, median (IQR)	39 (32-47)	44 (34-58)
First primary cancer diagnosis, *n* (%)[e]	224 (100)	55 (100)
Breast cancer, *n* (%)	129 (58)	1 (2)
Thyroid cancer, *n* (%)	33 (15)	14 (25)
Endometrial cancer, *n* (%)	21 (9)	-
Colorectal cancer, *n* (%)	2 (1)	11 (20)
Renal cancer, *n* (%)	3 (1)	3 (5)
Melanoma, *n* (%)	9 (4)	5 (9)
Other, *n* (%)[e]	27 (12)	21 (38)
Age at first primary cancer diagnosis, *n* (%)[c]	223 (100)	55 (100)
Age, median (IQR)	39 (31-47)	44 (34-58)
Coding effect, *n* (%)[c]	224 (100)	54 (98)
Missense, *n* (%)	66 (29)	13 (24)
Truncating, *n* (%)	157 (70)	40 (74)
Other, *n* (%)	1 (0)	1 (2)
Domain, *n* (%)[c]	224 (100)	54 (98)
C2, *n* (%)	65 (29)	19 (35)
Phosphatase, *n* (%)	119 (53)	26 (48)
Other, *n* (%)	40 (18)	9 (17)

IQR, interquartile range; *PHTS*, PTEN Hamartoma Tumor Syndrome.

[a]Percentage of the total cohort.

[b]The index patient is the first patient in a family to be diagnosed with PHTS and to undergo genetic germline testing of *PTEN* based on clinical suspicion (Supplemental methods).

[c]Availability of information.

[d]IQR (ie, quantile 1 to quantile 3).

[e]Other cancer diagnoses were, eg, basal cell carcinoma, in situ melanoma, prostate cancer, lung cancer, ovarian cancer, glioblastoma, and Hodgkin lymphoma.

in females and 46 years (IQR = 36-56) in males. Most females had a PHTS-related cancer diagnosis (93%) and the median age at the first PHTS-related cancer diagnosis was 39 years (IQR = 32-47). A PHTS-related cancer was diagnosed in 67% of males with a median age at first PHTS-related cancer diagnosis of 44 years (IQR = 34-58). Females developed BC most often (161/224, 72%). Of these patients, 108/161 (67%) had multiple primary cancers. Males developed TC most often (18/55, 33%). Of these patients, 7/18 (39%) had multiple primary cancers. Females and males both had a median follow-up time after first primary cancer of 5 years (IQR = 1-11 and 1-12, respectively). The majority of primary cancer diagnoses (377/505, 75%) were confirmed by pathology. The proportion of pathology-confirmed primary cancer diagnoses was comparable across countries.

Any second primary cancer

More than half of the patients (54%) developed a second primary cancer. Overall, the median time to a second primary cancer was 4.7 years (IQR = 0.4-11.0). Of females, 131 (58%) developed a second primary cancer. The median time to a second primary cancer was 4.1 years (IQR = 0.3-10.8). Nineteen (35%) males developed a second primary cancer with a median time to a second primary cancer of 8.0 years (IQR = 1.4-13.0).

In females, the 5-year second primary cancer risk was 28.0% (95% CI = 21.7-35.7), and the 10-year risk was 48.0% (95% CI = 39.8-57.0) (Figure 1A). In males, both 5-year and 10-year risks were lower with 13.9% (95% CI = 6.5-28.4) and 32.7% (95% CI = 19.0-52.6), respectively. When only patients with a first primary cancer predating their PHTS diagnosis were included in the analyses ($n = 189$), the 5-year risk was slightly lower with 27.1% (95% CI = 20.4-35.5) in females and 10.4% (95% CI = 3.5-28.8) in males; however, the number of males was low (Supplemental Figure 1A).

PHTS-related second primary cancer

Of females with a PHTS-related first primary cancer, 106/197 (54%) had a PHTS-related second primary cancer. The median time to second primary cancer was 4.4 years (IQR = 0.3-9.4). Of males, this was 10/34 (29%), with a median time to second primary cancer of 3.7 years (IQR = 0.5-13.2). This included 3 (30%) males with melanoma as first primary cancer and second primary cancer.

The 5-year risk of PHTS-related second primary cancer was 24.5% (95% CI = 18.1-32.5) and the 10-year risk was 45.7% (95% CI = 36.9-55.4) in females (Figure 1B). The majority (39/56) of females with a PHTS-related second primary cancer within 10 years after a PHTS-related first primary cancer had BC as a PHTS-related second primary cancer. In males, the 5- and 10-year risks for PHTS-related second primary cancer were 14.5% (95% CI = 5.7-34.1) and 19.8% (95% CI = 8.6-41.9), respectively. When only patients with PHTS-related first primary cancer predating their PHTS diagnosis were included in the analyses ($n = 158$), the 5-year risks were lower with 22.8% (95% CI = 16.2-31.6) in females and 5.9% (95% CI = 0.9-35.0) in males; however, the number of males was low (Supplemental Figure 1B).

Second primary BC

Of females with BC as first primary cancer, 69/129 (53%) developed a second primary BC, irrespective of laterality. Of females with multiple primary BCs, 23/69 (33%) were diagnosed with 2 primary BCs simultaneously at median age of 39 years (IQR = 34-46). These females were excluded from risk analyses. Importantly, 53% of the females with 2 primary BCs had both diagnoses predating their PHTS diagnosis. Furthermore, 51 females underwent bilateral mastectomies within 1 year after first primary BC diagnosis.

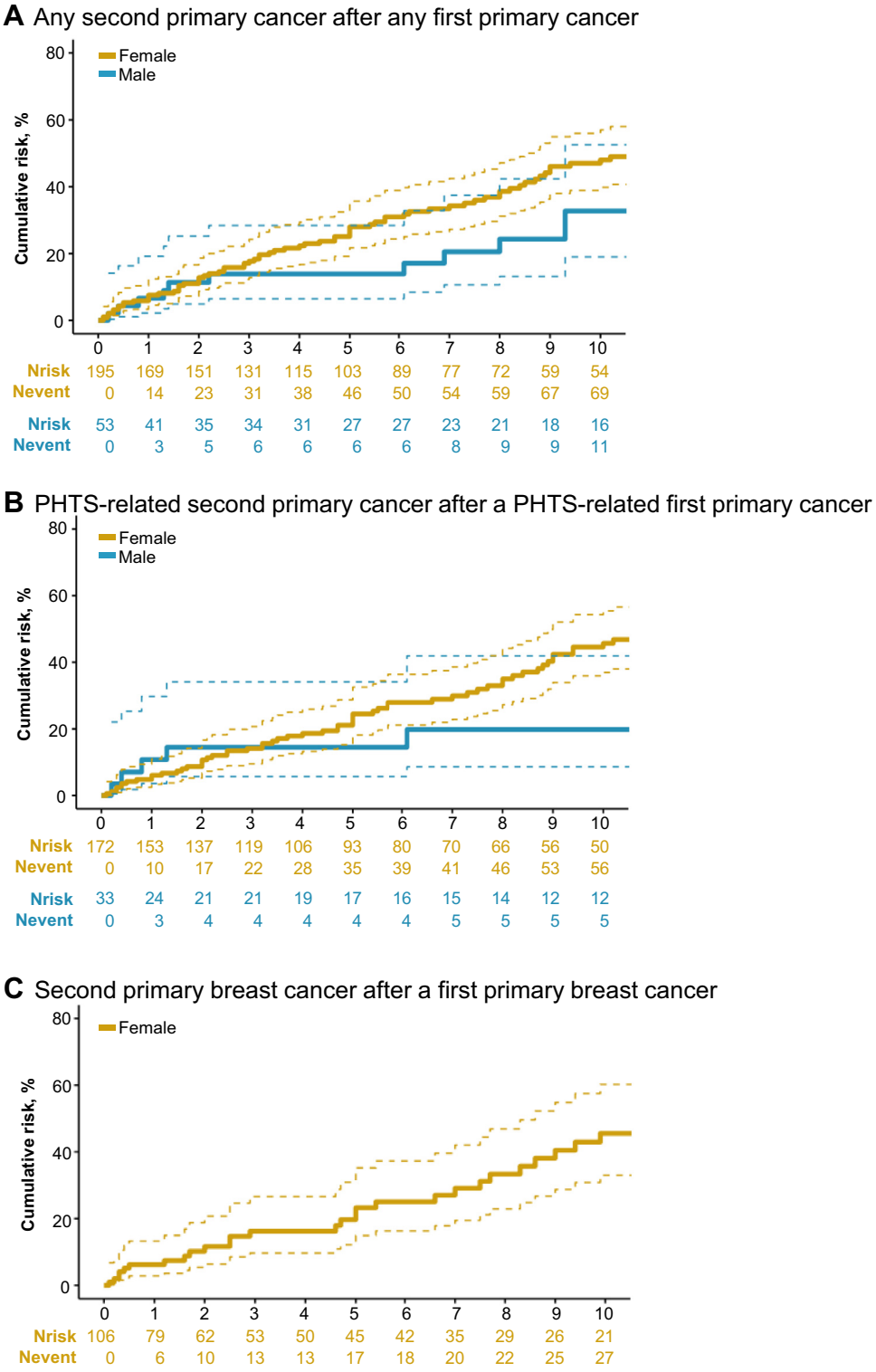

Figure 1 The cumulative risk of a second primary cancer. Risks for a second primary cancer are presented on the *y*-axis in percentages (%) for the years since first primary cancer diagnosis (*x*-axis). Dashed lines represent 95% confidence intervals. The number at risk (Nrisk) and the cumulative number of events (Nevent) are presented below the graphs. A. The risk of any second primary cancer after any first primary cancer diagnosis for females and males. B. The risk of a second primary PHTS-related cancer after a first primary PHTS-related cancer for females and males. In this cohort, the first primary cancer is a PHTS-related cancer. C. The risk of a second primary breast cancer after a first primary breast cancer for females. Breast cancer is the first primary cancer diagnosed in the patients. PHTS, PTEN Hamartoma Tumor Syndrome.

The risk of a second primary BC after a first primary BC was 23.3% (95% CI = 14.9-35.2) after 5 years and 45.6% (95% CI = 33.0-60.2) after 10 years (Figure 1C). In this group, the median time to second primary BC was 5.0 years (IQR = 1.7-9.0). The risk was lower when only females with first primary BC predating their PHTS diagnosis were included in the analyses ($n = 84$) with 22.5% (95% CI = 13.8-35.4) after 5 years. Median time to second primary cancer was 2.9 years (IQR = 0.0-8.4) (Supplemental Figure 1C).

Second primary BC risk after first primary BC was similar for patients with truncating versus missense variants (hazard ratio [HR] = 0.8, 95% CI = 0.3-2.0) (Supplemental Figure 2). Patients with variants in the phosphatase domain had a 2.5 times lower risk compared with domain C2 (HR = 0.4, 95% CI = 0.1-0.9).

Discussion

This large European cohort study demonstrated predominantly high second primary cancer risks for female patients in addition to previously reported high first primary cancer risks.[3] This high second primary cancer risk was mainly, but not exclusively, BC driven: the PHTS-related second primary cancer risk was 24.5% after 5 years and 45.7% after 10 years, and second primary BC risk after first primary BC was 23.3% after 5 years and 45.6% after 10 years. The PHTS-related second primary cancer risks for males were also high: the risk was 14.5% after 5 years and 19.8% after 10 years. These data emphasize the importance of recognizing patients before or at first primary cancer diagnosis to enable potential early cancer detection or prevention via surveillance or risk-reducing surgeries.[7-10]

The median interval to any second primary cancer after any first primary cancer was 4.1 years (IQR = 0.3-10.8) for females and 8.0 years (IQR = 1.4-13.0) for males. The median interval between the first and second primary PHTS-related cancer was 4.4 years (IQR = 0.3-9.4) for females and 3.7 years (IQR = 0.5-13.2) for males. These results for females are likely driven by the high risk of BC, whereas the more variable results for males may potentially be explained by the low number of males for analyses. Overall, multiple primary cancer development with 54% was more frequent than previously reported for the general population (2%-17%)[11-14] and for PHTS (25%-42%), with a substantially lower median interval from first primary cancer to second primary cancer compared with previous reports on PHTS (4.7 years versus 13.2 years).[4,5,15,16] This is potentially driven by early cancer detection due to PHTS-specific cancer surveillance, which was supported by higher second primary cancer risks for patients with their first primary cancer diagnosed after their PHTS diagnosis. Furthermore, the differences between cohorts could not be explained by differences in first primary cancer diagnostic age, first primary cancer diagnostic year, year of birth, coding effect, or domain (data not shown). Despite limited sample size, the lower second primary cancer stage for patients with first primary cancer after PHTS diagnosis supports earlier detection by surveillance.[9] These second primary cancer risks can be used to counsel patients with PHTS.

It is reported that the first primary BC risk presumably depends on the *PTEN* coding effect and domain.[3] No indication for different second primary BC risks based on coding effect was observed. Variants in the phosphatase domain may have lower second primary BC risks after first primary BC compared with variants in domain C2, whereas the effect was opposite for first primary BC.[3] Because the cohort containing females with first primary BC is a selection of the total PHTS population, it is presumable that this cohort might be enriched for a selection of variants with truncating or truncating-like activities.[3,17] However, underlying mechanisms or influencing factors remain unknown and require further evaluation.

Many females (>50%) with multiple primary BCs had a second primary BC predating their PHTS diagnosis. Together with the previously shown effectiveness of breast surveillance with MRI, this emphasizes the importance of improving early PHTS patient recognition and adherence to surveillance recommendations, even after first primary BC diagnosis.[9] In males, no specific combination of primary cancers was notable, and the advice remains to adhere to cancer surveillance recommendations.[18] Furthermore, the second primary BC risk after a first primary BC with 45.6% after 10 years was higher than previously reported for PHTS (29%)[4] and *BRCA1* pathogenic variant heterozygotes (13%-32%).[19-23] *BRCA1* pathogenic variant heterozygotes can opt for risk-reducing surgery because this has been associated with high survival.[24] Considering the previously reported high risks up to 76% by age 60 for first primary BC in females with PHTS, risk-reducing surgery should be offered similarly to patients with PHTS.[3]

Although the study cohort was large considering the rarity of PHTS and stratification for sex and timing of first primary cancer diagnosis was performed, the number of patients was too limited for subgroup analyses regarding patient and cancer characteristics. Furthermore, because competing risks were expected to be neglectable, we did not use a competing risk model, which may have led to slight overestimation of the risk estimates. These limitations could be addressed in a larger prospective longitudinal cohort study, but because of the rarity of PHTS, this is challenging to accomplish in the foreseeable future.

This large European cohort study demonstrated that all patients with PHTS have high second primary cancer risks. Females have high second primary cancer risks that are largely, but not exclusively, driven by second primary BC. Early PHTS recognition should be improved because timely breast surveillance can be lifesaving. Furthermore, risk-reducing breast surgery should be offered, and surveillance should be continued after first primary BC diagnosis. Together, these results underscore the importance of recognizing patients before or at first primary cancer diagnosis to facilitate potential early detection or prevention of

second primary cancer through surveillance or risk-reducing surgery for PHTS-related cancers in both male and female patients with PHTS.

Data Availability

Individual patient data cannot be shared because of privacy and ethical considerations. Requests for aggregate study data can be submitted to the corresponding author.

Acknowledgments

This research is supported (not financially) by the European Reference Network on Genetic Tumor Risk Syndromes - Project identification number 739547. European Reference Network on Genetic Tumor Risk Syndromes is partly cofunded by the European Union within the framework of the Third Health Program "ERN-2016 - Framework Partnership Agreement 2017-2021." M.T. was supported by the National Institute for Health and Care Research Cambridge Biomedical Research Centre (NIHR203312).

The authors thank the Dutch Nationwide Pathology Databank (PALGA) for retrieval of the pathology data and contribution to this study, and The Netherlands Comprehensive Cancer Organization (IKNL) for the collection of data for The Netherlands Cancer Registry.

Funding

This work has been funded, in part, by the PTEN Research Foundation, a charity governed by English law (charity number 117358) to L.A.J.H. and J.R.V. under grant number RUM 17-002 and the European Union under Horizon Europe to K.C.J.V. under grant number 101095483.

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Ethics Declaration

This study was performed in accordance with the Declaration of Helsinki. The Research Ethics Committee of the Radboud university medical center (file number 2018-5056) approved this study and the institutional ethics committees approved this study. Written informed consent was obtained when indicated by the ethics committee.

Conflict of Interest

Arjen R. Mensenkamp received funds from AstraZeneca for contribution to sponsored quality assessment and variant interpretation of variants of uncertain significance in *BRCA1* and *BRCA2*. This funding was not related to this study. Judith Balmaña received funding support from GSK for an educational activity unrelated to this study. Arne Jahn received an honorarium from AstraZeneca for work unrelated to this study. All other authors declare no conflicts of interest.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gim.2025.101467) contains supplemental material, which is available to authorized users.

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