MINIREVIEW

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A review on age-related cancer risks in PTEN hamartoma tumor syndrome

Linda A.J. Hendricks[1,2] | Nicoline Hoogerbrugge[1,3] |
Janneke H.M. Schuurs-Hoeijmakers[1] | Janet R. Vos[1,2]

[1]Department of Human Genetics, Radboud university medical center, Nijmegen, The Netherlands

[2]Radboud university medical center, Radboud Institute for Health Sciences, Nijmegen, The Netherlands

[3]Radboud university medical center, Radboud Institute for Molecular Life Sciences, Nijmegen, The Netherlands

Correspondence
Janet R. Vos, Department of Human Genetics, Radboud university medical center, P.O. Box 9101, 6500 HB, Nijmegen, The Netherlands.
Email: janet.vos@radboudumc.nl

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Abstract

Patients with PTEN hamartoma tumor syndrome (PHTS, comprising Cowden, Bannayan-Riley-Ruvalcaba, and Proteus-like syndromes) are at increased risk of developing cancer due to pathogenic *PTEN* germline variants. This review summarizes age-, sex-, and type-specific malignant cancer risks for PHTS patients, which is urgently needed for clinical management. A PubMed literature search for Standardized Incidence Ratios or Cumulative Lifetime cancer risks (CLTRs) resulted in nine cohort studies comprising four independent PHTS cohorts, including mainly index cases and prevalent cancer cases. The median age at diagnosis was 36 years. Reported CLTRs for any cancer varied from 81% to 90%. The tumor spectrum included female breast cancer (CLTRs including sex-specific estimates at age 60-70: 67% to 85%), endometrium cancer (19% to 28%), thyroid cancer (6% to 38%), renal cancer (2% to 24%), colorectal cancer (9% to 32%), and melanoma (0% to 6%). Although these estimates provide guidance for clinical care, discrepancies between studies, sample sizes, retrospective designs, strongly ascertained cases, and lack of pediatric research emphasizes that data should be interpreted with great caution. Therefore, more accurate and more personalized age-, sex-, and cancer-specific risk estimates are needed to enable counseling of all PHTS patients irrespective of ascertainment, and improvement of cancer surveillance guidelines.

KEYWORDS
germ-line mutation, Hamartoma syndrome, multiple, neoplasms, neoplastic syndromes, hereditary, PTEN Phosphohydrolase, risk

1 | INTRODUCTION

PTEN hamartoma tumor syndrome (PHTS) is associated with strong increased lifetime risks for several cancer types due to pathogenic germline variants in the tumor suppressor gene *PTEN*. Additionally, PHTS is associated with developmental delay, complex and multifaced overgrowth phenotypes, including macrocephaly, benign tumors, and skin abnormalities.[1] The current available prevalence estimate of 1 in 200 000 is likely underestimated as the majority of patients are not recognized as such.[2-4]

Accurate cancer risk estimates have considerable importance for patients, genetic counseling, cancer risk management, and treatment. However, current PHTS cancer risk estimates are under debate and a criterial overview is lacking.[5,6] Current PHTS surveillance guidelines

advise (bi)annual screening for breast cancer (BC), thyroid cancer (TC), and renal cancer (RC) with little variation in starting age and screening modality. While endometrial cancer (EC), colorectal cancer (CRC) and melanoma surveillance varies from none to annual screening.[7,8]

In this review, we provide data on PHTS age-related, sex-specific, and type-specific malignant cancer risks, and identify aspects that need further investigation for evidence-based cancer risk management of PHTS patients.

2 | METHODS

A PubMed search was conducted to identify cohort studies on cancer risk estimates in PHTS patients using keywords: ("PTEN Hamartoma Tumor Syndrome" OR "germline *PTEN*") AND "cancer" (Supplementary Figure 1). Case-control studies were excluded because sample sizes are too limited to detect rare germline variants in both cases and controls.[9] Study quality was evaluated on common cancer risk estimate variation sources: methodology, patient recruitment, and population characteristics.[10] Overlapping cohorts were included because they provided complementary approaches or outcomes. First cancers were defined as first type-specific cancers, and second cancers as first type-specific cancers after any other cancer.

Cumulative Lifetime Risks (CLTRs) and Standardized Incidence Ratios (SIRs) were extracted with corresponding 95% Confidence Interval (95%CI) if available. By absence of exact values, data were extracted manually from figures. The (prospective) years of follow-up and number of patients at risk per age group were missing and could not be extracted. For reference, cancer risks in the Dutch general population were presented.[11]

3 | RESULTS

3.1 | Selected studies

Nine studies, including four independent cohorts, described cancer risks for PHTS patients, published between 2010 and 2014 (Supplementary Figure 1, Supplementary Table 1). Eight studies presented risks for first cancers and one for second cancers.[12] All exclusively included patients with confirmed *PTEN* pathogenic germline variants except one (46% confirmed).[13] Cohorts included 114 to 368 PHTS patients, mainly European and American, comprised 20% to 52% males and 27% to 30% under 18 years.

Most cohorts were clinic-based and ascertained by *PTEN* mutation status or PHTS-associated clinical characteristics, including cancer. Cohorts included up to 65% to 100% index patients (i.e. clinically affected individuals with the indication to start genetic testing in the family). For all studies assessing first cancer risks, the observation period was for each cancer type from date of birth, until cancer diagnosis, death, or moment of last contact, whichever came first. Most cancers were clinically or pathologically confirmed. Because cancers both before and after DNA diagnosis were included, ascertainment bias likely affected cohorts by over-estimating risks.

3.2 | Overall risk

Both female and male PHTS patients have increased lifetime cancer risks. For females, this is relatively higher due to frequent female cancers (BC and EC).[5,13,14] SIRs reported for females and males were 22.9 (95%CI 16.0-31.7) and 11.9 (95%CI 7.5-17.9), respectively (Figure 1(A)).[14] Female CLTR ranged from 5%-8% at age 20 to 85%-90% at age 70, compared with 0%-7% at age 20 and 81%-88% at age 70 in males (Figure 2(A)).[5,13,14] Although two out of three studies reporting overall risks included Lhermitte-Duclos Disease, a severe (benign) brain tumor, no systematic differences between risk estimates were observed.[5,13,14]

The median age of cancer diagnosis was 36 years,[14] compared with 68 years in the general population.[11] The highest cumulative percentage increase in a decade in females was observed between age 40 and 50 (+31-32%) and in males from age 50 to 60 onwards (+12-29%).[5,13,14]

In patients with cancer, the risk to develop a second cancer was 8 times (95%CI 6-10) increased compared with the general population, and was diagnosed within a median interval of 5 years after first cancer diagnosis.[12]

3.3 | Breast cancer

The female BC risk is significantly increased in PHTS with SIR point estimates of 22 to 39 (Figure 1(B)).[6,14,15] CLTR at age 30 ranged from 2% to 8% and at age 70 from 77% to 85% (Figure 2(B)).[5,6,13,14] The median age of female BC diagnosis was 42 years,[14] compared with 63 years in the general population.[11] The youngest age at diagnosis was 21 to 27 years,[6,13,14] and the strongest cumulative percentage increase in a decade was reported between 40 and 50 years (+29%-50%).[5,6,13,14] About 25% to 48% of female BC was bilateral, being more frequent than in the general population (0.8%-3%).[5,13,14,16]

The risk to develop female BC as second cancer was 9 times (95%CI 6-13) increased compared with the general population. The CLTR increased from 1% at age 40 to 40% at age 70. The median age of diagnosis was 52 years (range 39-71). The risk on second BC increased from 1 year after first BC diagnosis onwards, to nearly 90% after 37 years.[12]

3.4 | Endometrial cancer

The EC risk in PHTS is over 40 times increased compared with the general population (SIR 43-49) (Figure 1(C)).[6,14] However, confidence intervals are wide (95%CI 28-63 and 10-142) due to low number of EC cases (Table 1).[6,14] CLTR ranged from 0% to 1% at age 20, 1% to 2% at age 30 and 19% to 28% at age 70 (Figure 2(C)).[5,6,13] The median age at EC diagnosis was 48 years,[14] compared with 68 years in the
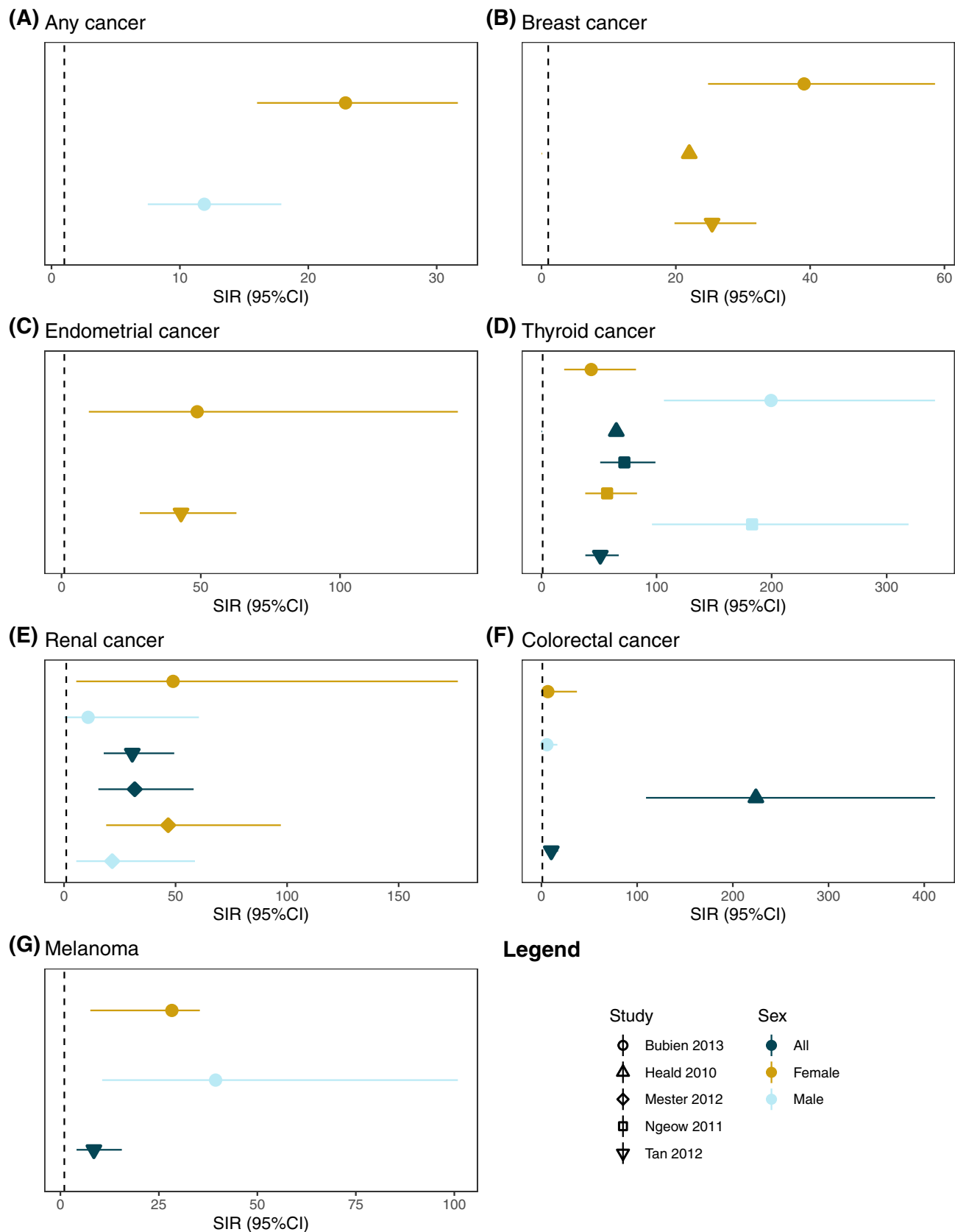
FIGURE 1 **Standardized Incidence Ratios per cancer type in PHTS patients.** The Standardized Incidence Ratio (SIR) is presented with corresponding 95% Confidence Interval (95%CI) on the x-axis. Shapes represent different studies and colors different sexes. The vertical dashed line represents SIR = 1.0. SIRs are presented for (A) any cancer, (B) female breast cancer, (C) endometrial cancer, (D) thyroid cancer, (E) renal cancer, (F) colorectal cancer, (G) melanoma [Colour figure can be viewed at wileyonlinelibrary.com]

(A)

Any cancer

(B)

Breast cancer

(C)

Endometrial cancer

(D)

Thyroid cancer

(E)

Renal cancer

(F)

Colorectal cancer

(G)

Melanoma

Legend

Study
- ◆ As reference general population
- ⬭ Bubien 2013
- ✕ Nieuwenhuis 2012
- ✛ Nieuwenhuis 2014
- ✳ Riegert–Johnson 2010
- ▽ Tan 2012

Sex
- ● All
- ● Female
- ● Male

FIGURE 2 Cumulative Lifetime Risks per cancer type in PHTS patients. The Cumulative Lifetime Risk (CLTR) is presented in percentages per age-group with corresponding 95% Confidence Interval (95%CI) on the y-axis. Shapes represent different studies and colors different sexes. CLTRs are presented for (A) any cancer (Nieuwenhuis et al. [2014] and Riegert-Johnson et al. included Lhermitte-Duclos Disease),[5,13] (B) female breast cancer, (C) endometrial cancer, (D) thyroid cancer, (E) renal cancer, (F) colorectal cancer, (G) melanoma [Colour figure can be viewed at wileyonlinelibrary.com]
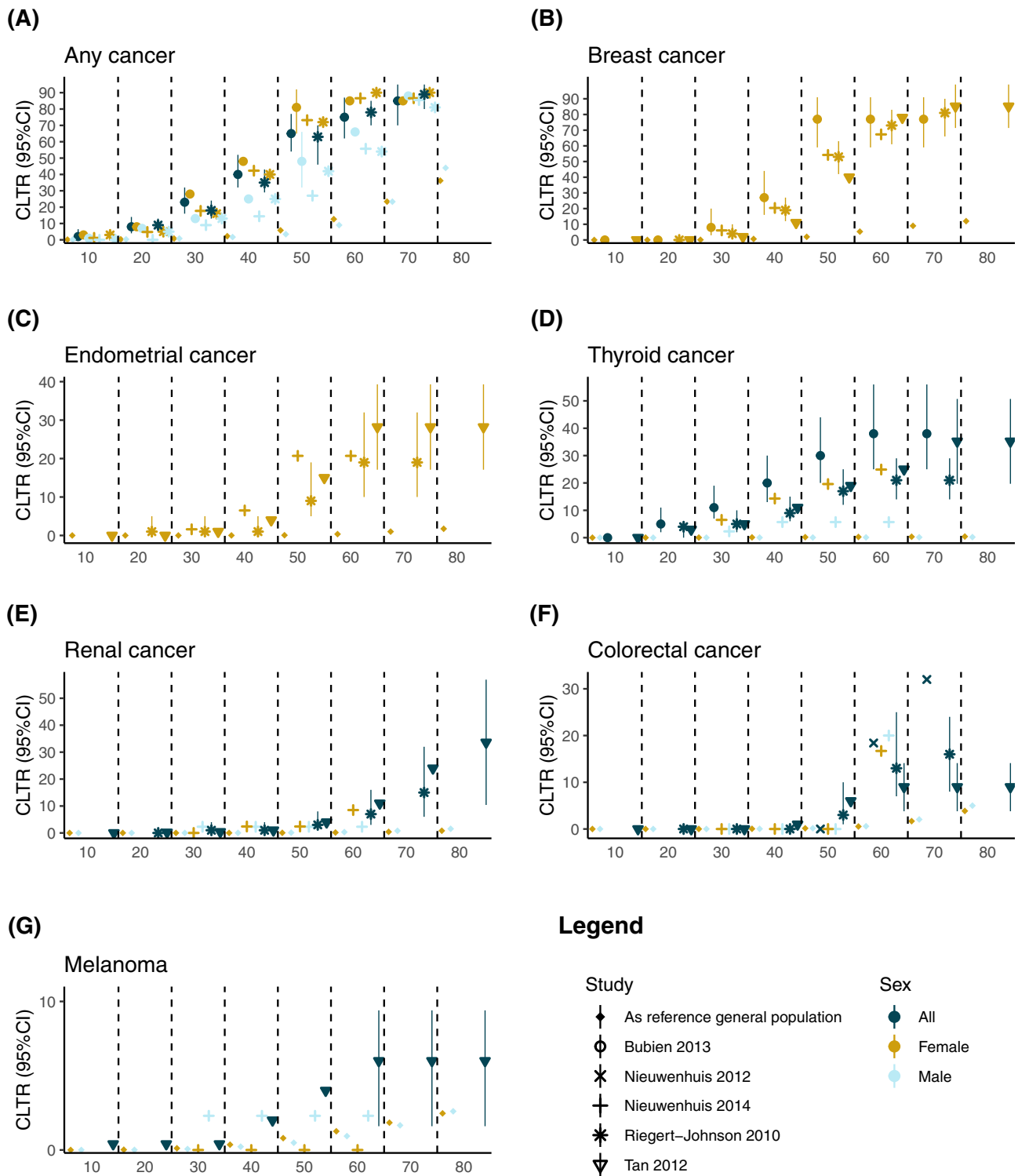
general population.[11] The youngest age at diagnosis was 21 to 33 years,[6,13,14] and the strongest cumulative percentage increase in a decade was reported between age 40 and 50 (+8-14%).[5,6,13]

In patients with cancer, the risk to develop EC as second cancer was 15 times (95%CI 7-27) increased compared with the general population. The CLTR was 50% at age 70.[12]

TABLE 1 PHTS patients at risk and observed cancers[a]

	Any	BC	EC	TC	RC	CRC	Melanoma
Bubien et al.[14]							
Total (n/N)	59/146	—	—	22/146	3/146	4/146	8/146
Female (n/N)	36/70	23/70	3/70	9/70	2/70	1/70	4/70
Male (n/N)	23/76	—	—	13/76	1/76	3/76	4/76
Riegert-Johnson et al.[13]							
Total (n/N)	130/211						
Female (n/N)	95/136	61/136	12/136	23/136	5/136	5/136	—
Male (n/N)	35/75	2/75	—	5/75	3/75	5/75	—
Nieuwenhuis et al. (2012)[19]							
Total (n/N)	—	—	—	—	—	4/156	—
Female (n/N)	—	—	—	—	—	2/89	—
Male (n/N)	—	—	—	—	—	2/67	—
Nieuwenhuis et al. (2014)[5]							
Total (n/N)	56/180	24/180	—	14/180	4/180	4/180	1/180
Female (n/N)	42/99	24/99	7/99	12/99	2/99	2/99	0/99
Male (n/N)	14/81	0/81	—	2/81	2/81	2/81	1/81
Heald et al.[15]							
Total (n/N)	—	—	—	21/127	—	9/127	—
Female (n/N)	—	24/64	8/64	—	—	5/64	—
Male (n/N)	—	—	—	—	—	4/63	—
Ngeow et al. (2011)[17]							
Total (n/N)	—	—	—	36/174	—	—	—
Female (n/N)	—	—	—	25/?	—	—	—
Male (n/N)	—	—	—	11/?	—	—	—
Tan et al.[6]							
Total (n/N)	—	—	—	48/368	15/368	12/368	9/368
Female (n/N)	—	67/205	24/205	—	—	—	—
Male (n/N)	—	—	—	—	—	—	—
Mester et al.[18]							
Total (n/N)	—	—	—	—	9/219	—	—
Female (n/N)	—	—	—	—	6/?	—	—
Male (n/N)	—	—	—	—	3/?	—	—
Ngeow et al. (2014)[12]							
Total (n/N)	52/114	—	—	12/114	2/114	3/114	2/114
Female (n/N)	—	24/91	10/91	—	—	—	—
Male (n/N)	—	—	—	—	—	—	—

[a]Number of PHTS patients at risk (N) and observed PHTS patients with cancer (n) are presented for any type of cancer (Any), breast cancer (BC), endometrial cancer (EC), thyroid cancer (TC), renal cancer (RC), colorectal cancer (CRC), and melanoma for the included studies.

3.5 | Thyroid cancer

TC risk is 51 to 72 times increased in PHTS compared with the general population.[6,15,17] In males, the TC risk was stronger increased (SIR 183-200) than in females (SIR 43-57) (Figure 1 (D)).[14,17] Overall CLTRs increased gradually from 3% to 5% at age 20 to 21% to 38% at age 70, with females following this trend with CLTR of 25% at age 60. For males, the CLTR remained stable at 6% from age 40 onwards, though this was only based on 2 cancer cases, and limited follow-up time at older ages likely hampered accurate risk estimation (Figure 2(D)).[5,6,13,14] The median age at diagnosis was 31 to 37 years,[14,17] compared with 53 years in the general population.[11] TC can present pediatrically with the earliest diagnosis from 7 to 16 years,[6,13,14,17] and the highest cumulative percentage increase in a decade was reported between age 40 and 50 (+8-10%).[6,13,14]

The risk to develop TC as second cancer was 6 times (95%CI 3-10) increased compared with the general population. CLTR was 2% at age 50 and 8% at age 70.[12]

3.6 | Renal cancer

The RC risk is 31 to 32 times increased in PHTS. The female risk is stronger increased compared with males (SIR 47-49 vs. 11-22, respectively) (Figure 1(E)).[6,14,18] However, wide confidence intervals reflect few observed RC cases. CLTR at age 20 ranged from 0% to 0.2% and from 15% to 24% at age 70, with male CLTR at age 60 of 2% and female of 9% (Figure 2(E)).[5,6,13] The median age at diagnosis was 49 to 55 years,[14,18] compared to 68 years in the general population.[11] The youngest age at RC diagnoses was 11 to 31 years[6,13,14,18] and the highest cumulative percentage increase in a decade was reported between age 60 and 70 (+8-13%).[6,13]

The risk to develop RC as second cancer was not significantly increased (SIR 4, 95%CI 0.5-14.8) compared with the general population. The CLTR at age 70 was 20%.[12]

3.7 | Colorectal cancer

The CRC risk in PHTS might be increased compared with the general population. However, SIRs have wide confidence intervals and estimates are highly deviating from 10[6] to 224[15] and sex-specific SIRs were 6 and 7 for males and females, respectively[14] (Figure 1(F)). The highest estimate likely resulted from ascertainment bias, regarding the selected cohort on gastrointestinal lesions.[15] The CLTR at age 40 ranged from 0% to 1% and from 9% to 32% at age 70.[6,13,19] Males and females report CLTRs of 20% and 17% at age 60, respectively[5] (Figure 2(F)). The median age at diagnosis was 46 to 58 years in PHTS,[14,19] compared with 73 years in the general population.[11] The youngest age at diagnosis was 32 to 53 years[6,13-15,19] and the highest cumulative percentage increase in a decade was reported between age 50 and 60 (+2-18%).[5,6,13,19]

The risk to develop CRC as second cancer was 6 times (95%CI 1.3-18) increased compared with the general population.[12]

3.8 | Melanoma

The risk of melanoma in PHTS is possibly increased compared with the general population, but data is limited. Studies observed none or only few melanoma cases. Reported risk increases are 9, 28, and 39 times for the total population,[6] females, and males, respectively[14] (Figure 1(G)). The CLTR for melanoma gradually increased from 0.4% at age 20 to 6% at age 70 (Figure 2(G)).[6] Males and females report CLTR of 2% and 0% at age 60, respectively.[5] The median age at diagnosis was 40 years,[14] compared with 63 years in the general population.[11] The youngest age at diagnosis was 3 to 27.[5,6,14]

The risk to develop melanoma as second cancer was 7 times (95% CI 1.2-25) increased compared with the general population.[12]

3.9 | Other cancers

Limited information was available for other cancers not associated with the PHTS tumor spectrum. Risk estimates for lung and gastric cancer were provided on only three and one case(s), respectively.[5,15] Additionally skin, ovary, testicular, ethmoid, vocal cord, parotid, and anal squamous cell cancer, seminoma, carcinoid, trichilemmal carcinoma, prostate adenocarcinoma, hepatocellular carcinoma, and transitional cell carcinoma of the bladder were reported without risk estimates.[5,13,14]

4 | DISCUSSION

This review summarizes evidence on cancer risks and development by age in PHTS patients. Given the current available cancer risk estimates, female PHTS patients have an increased risk and earlier onset of female breast, endometrial and thyroid cancer compared with the general population, while male PHTS patients have an increased risk of thyroid cancer. For other cancers, the risks remain to be defined more accurately. Overall, cancer risks are rather uncertain and probably overestimated due to uncorrected ascertainment bias (e.g. inclusion of index cases and prevalent cancer cases), discrepancies between studies, small sample sizes, and limited follow-up time. The broad phenotypic spectrum of PHTS and its likely higher prevalence underline the need for more accurate and personalized age-, sex-, and type-specific cancer risks. Therefore, current risks should be interpreted with caution. They are not generalizable to all PHTS patients and ascertainment should be considered when using these risks. Especially, for unselected PHTS patients the cancer risks are yet unknown, though likely lower than those currently available.

Identification of bias and study heterogeneity is essential for future risk estimate improvement. As various cohorts overlap and are mainly European and American with similar analyses, population and methodological factors likely do not explain observed risk variations. International differences between population surveillance, diagnostic criteria for clinical referral, and patient surveillance after diagnosis could contribute to detection differences of incident and prevalent cancers. However, the impact of surveillance differences on detected cancers likely remains limited, since all studies included also prevalent cases. Although no studies on first cancers addressed risk-reducing surgeries (e.g. mastectomies), potential risk underestimation is likely minimal regarding mainly retrospective designs and current PHTS guidelines. Furthermore, it was unclear whether active informed consent was always required at study initiation, potentially inducing survival bias and reduced or delayed cancer risk increases in time. Although wide confidence intervals observed are related to low sample sizes and number of cancers, not addressing potential presence of familial clustering might led to underestimated widths. American and

(non-)Western collaborative efforts are needed for larger follow-up cohorts with additional inclusion of relatives with a pathogenic germline *PTEN* variant.

This review supports breast and thyroid cancer surveillance as proposed by current European and American guidelines.[7,8] Additional endometrial surveillance is supported, although not advised regarding efficacy by European guidelines.[7] For other cancers, data are even more scarce and evidence should be generated for surveillance advice.

In conclusion, overall evidently increased risks and earlier onset of female breast, endometrial, and thyroid cancer are observed in PHTS patients. However, current risks are likely overestimated by ascertainment bias. To enable optimal counseling and risk-based surveillance of all PHTS patients irrespective of ascertainment, prospective cohort studies with substantial follow-up of all ethnicities are needed to obtain more accurate and personalized age-, sex-, and type-specific cancer risk estimates.

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CONFLICT OF INTEREST
The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable since no new data were created.

ORCID
Linda A.J. Hendricks https://orcid.org/0000-0002-1008-0265
Nicoline Hoogerbrugge https://orcid.org/0000-0003-2393-8141
Janet R. Vos https://orcid.org/0000-0001-8802-7002

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SUPPORTING INFORMATION
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