

Supplementary Tables and Figures

Supplement to:

Hendricks LAJ, Hoogerbrugge N, Mensenkamp AR, Brunet J, Lleuger-Pujol R, Høberg-Vetti H, Tveit Haavind M, Innella G, Turchetti D, Aretz S, Spier I, Tischkowitz M, Jahn A, Links TP, Olderode-Berends MJW, Blatnik A, Leter EM, Evans DG, Woodward ER, Steinke-Lange V, Anastasiadou VC, Colas C, Villy M, Benusiglio PR, Gerasimenko A, Barili V, Branchaud M, Houdayer C, Tesi B, Yazicioglu MO, Van der Post RS, Schuurs-Hoeijmakers JHM, PTEN Study Group, Vos JR. *Cancer risks by sex and variant type in PTEN Hamartoma Tumor Syndrome*. J Natl Cancer Inst. 2022.

Supplementary Tables

Supplementary table 1. Definition of coding effect

Coding effect category	Definition
Truncating or predicted truncating	Frameshift, nonsense, start-loss, large structural variants (deletions of (the majority) of ≥ 1 exon), splice-site variants (± 5 base pairs (bp) of intron/exon boundary), and cryptic splice site variants
Missense	Missense and in-frame variants
Other	Variants in 5'- and 3'-UTR regions, synonymous variants, and intronic variants exceeding intron/exon boundary with more than 5bp

Supplementary table 2. Definition of PTEN protein domains

Protein domain	Boundaries in amino acids
Phosphatase Binding Domain (PBD)	1-6
Phosphatase Domain (PD)	7-185
C2 domain (C2)	186-351
C-terminal Region (CTR)	352-400
PDZ domain (PDZ)	401-403
Other, including PBD, CTR, PDZ	Variants spanning multiple domains, not located in a domain, or located in domains other than PD or C2 were grouped.

Supplementary table 3. Cancer characteristics per cohort and sex

	Prevalent cases in cohort including ca-index patients			Prevalent cases in cohort excluding ca-index patients			Incident cases in cohort including ca-index patients		
	N (%)	Median age (IQR)	Youngest age	N (%)	Median age (IQR)	Youngest age	N (%)	Median age (IQR)	Youngest age
Females	N = 281			N = 195			N = 240		
Any cancer ^a	159 (56.6)	40 (33-48)	8	74 (37.9)	43 (33-50)	12	33 (13.8)	43 (36-49)	17
Basal cell carcinoma	14 (5.0)	49 (42-53)	33	6 (3.1)	49 (42-51)	34	7 (2.9)	51 (49-54)	49
Bladder	0 (0.0)	-	-	0 (0.0)	-	-	0 (0.0)	-	-
Brain	5 (1.8)	46 (34-54)	12	4 (2.1)	50 (38-60)	12	3 (1.3)	46, 54, 76	46
Breast (including in situ)	115 (40.9)	42 (37-49)	23	50 (25.6)	43 (38-50)	26	30 (12.5)	42 (37-48)	26
In situ	33 (28.7)	38 (33-42)	23	16 (32.0)	38 (33-41)	26	15 (50.0)	38 (34-42)	26
Ductal	58 (50.4)	44 (38-50)	24	19 (38.0)	46 (40-52)	30	10 (33.3)	49 (42-52)	33
Lobular	2 (1.7)	48, 49	48	1 (2.0)	48	48	0 (0.0)	-	-
Adenocarcinoma	2 (1.7)	27, 49	27	2 (4.0)	27, 49	27	0 (0.0)	-	-
Not specified/other	20 (17.4)	43 (37-50)	26	12 (24.0)	45 (42-51)	36	5 (16.7)	43 (42-47)	36
Colorectal cancer	9 (3.2)	58 (52-61)	28	2 (1.0)	56, 61	56	3 (1.3)	56, 58, 61	56
Colorectal cancer or adenomatous polyps	50 (17.8)	48 (42-56)	22	24 (12.3)	50 (40-56)	22	29 (12.1)	48 (42-56)	25
Haematological	2 (0.7)	25, 57	25	1 (0.5)	25	25	0 (0.0)	-	-
Lung	8 (2.8)	57 (42-72)	37	3 (1.5)	37, 43, 74	37	4 (1.7)	57 (53-61)	43
Melanoma	11 (3.9)	36 (30-41)	26	6 (3.1)	30 (27-37)	26	3 (1.3)	28, 50, 62	28
Renal	4 (1.4)	42 (33-54)	33	2 (1.0)	33, 51	33	1 (0.4)	33	33
Stomach	2 (0.7)	47, 76	47	0 (0.0)	-	-	0 (0.0)	-	-
Thyroid	33 (11.7)	38 (25-47)	9	13 (6.7)	40 (28-48)	17	9 (3.8)	41 (36-46)	17
Follicular	11 (33.3)	25 (21-33)	14	3 (23.1)	22, 40, 75	22	2 (22.2)	22, 75	22
Papillary	14 (42.4)	42 (34-48)	22	7 (53.8)	43 (32-47)	22	5 (55.6)	43 (41-46)	36
Follicular papillary	4 (12.1)	37 (30-39)	17	1 (7.7)	17	17	2 (22.2)	17, 40	17
Anaplastic	1 (3.0)	63	63	1 (7.7)	63	63	0 (0.0)	-	-
Medullary	1 (3.0)	61	61	0 (0.0)	-	-	0 (0.0)	-	-
Not specified	2 (6.1)	9, 38	9	1 (7.7)	38	38	0 (0.0)	-	-
Female genitalia									
Cervix	1 (0.4)	56	56	1 (0.5)	56	49	0 (0.0)	-	-
Endometrial	25 (8.9)	47 (41-52)	23	13 (6.7)	49 (47-60)	23	3 (1.3)	40, 42, 50	40
Endometrioid ^b	12 (48.0)	49 (44-53)	41	6 (46.2)	54 (50-59)	48	1 (33.3)	50	50
Adenocarcinoma	4 (16.0)	47 (42-51)	26	1 (7.7)	47	47	0 (0.0)	-	-
Adenosquamous	1 (4.0)	40	40	0 (0.0)	-	-	0 (0.0)	-	-
Not specified	8 (32.0)	41 (33-50)	23	6 (46.2)	44 (30-57)	23	2 (66.7)	40, 42	40
Ovarian ^c	9 (3.2)	47 (23-49)	8	4 (2.1)	38 (27-48)	23	0 (0.0)	-	-

Males	N = 174			N = 152			N = 132		
Any cancer ^a	39 (22.4)	42 (28-55)	17	21 (13.8)	51 (30-64)	17	7 (5.3)	56 (51-64)	43
Basal cell carcinoma	5 (2.9)	66 (54-71)	44	3 (2.0)	71 (69-75)	66	1 (0.8)	78	78
Bladder	1 (0.6)	69	69	0 (0.0)	-	-	1 (0.8)	69	69
Brain	3 (1.7)	28, 28, 56	28	1 (0.7)	56	56	1 (0.8)	56	56
Breast (including in situ)	0 (0.0)	-	-	0 (0.0)	-	-	0 (0.0)	-	-
Colorectal cancer	7 (4.0)	43 (40-56)	38	2 (1.3)	43, 74	43	1 (0.8)	65	65
Colorectal cancer or adenomatous polyps	29 (16.7)	46 (42-61)	31	21 (13.8)	47 (43-61)	31	8 (6.1)	53 (46-59)	42
Haematological	4 (2.3)	51 (47-53)	36	3 (2.0)	51, 51, 60	51	2 (2.3)	51, 51	51
Lung	1 (0.6)	76	76	1 (0.7)	76	76	0 (0.0)	-	-
Melanoma	6 (3.4)	36 (27-53)	20	3 (2.0)	20, 30, 58	20	1 (0.8)	56	56
Renal	4 (2.3)	53 (44-57)	27	1 (0.7)	57	57	3 (2.3)	49, 57, 58	49
Stomach	0 (0.0)	-	-	0 (0.0)	-	-	0 (0.0)	-	-
Thyroid	12 (6.9)	39 (32-45)	17	5 (3.3)	43 (34-45)	17	3 (2.3)	43, 45, 52	43
Follicular	6 (50.0)	39 (35-42)	17	3 (60.0)	17, 34, 43	17	2 (66.7)	43, 52	43
Papillary	2 (16.7)	20, 39	20	0 (0.0)	-	-	0 (0.0)	-	-
Follicular papillary	1 (8.3)	52	52	1 (20.0)	52	52	0 (0.0)	-	-
Anaplastic	1 (8.3)	45	45	0 (0.0)	-	-	0 (0.0)	-	-
Medullary	0 (0.0)	-	-	0 (0.0)	-	-	0 (0.0)	-	-
Not specified	2 (16.7)	25, 45	25	1 (20.0)	45	45	1 (33.3)	45	45
Male genitalia									
Prostate	6 (3.4)	67 (65-70)	53	4 (2.6)	69 (67-73)	64	2 (1.5)	68, 70	68
Testis	3 (1.7)	24, 24, 26	24	3 (2.0)	24, 24, 26	24	0 (0.0)	-	-

^a Any cancer is comprised of all primary cancers depicted in this table, including in situ carcinomas, but excluding adenomatous polyps.; ^b Including adenoid adenocarcinoma.; ^c Ovarian cancer includes both cancer in the ovaries and/or fallopian tube(s).; IQR = interquartile range

Supplementary table 4. Surgery characteristics per cohort and sex ^a

	Prevalent cases in cohort including ca-index patients			Prevalent cases in cohort excluding ca-index patients			Incident cases in cohort including ca-index patients		
	N (%)	Median age (IQR)	Youngest age	N (%)	Median age (IQR)	Youngest age	N (%)	Median age (IQR)	Youngest age
Females		N = 281			N = 195			N = 240	
Thyroidectomy	87 (31.0)	38 (26-46)	8	47 (24.1)	31 (25-41)	9	32 (13.3)	41 (31-49)	16
Bilateral mastectomy	51 (18.1)	37 (32-42)	18	37 (19.0)	35 (31-42)	18	32 (13.3)	35 (31-42)	18
Hysterectomy	75 (26.7)	47 (40-51)	23	41 (21.0)	47 (41-52)	20	32 (13.3)	46 (40-50)	30
Bilateral ovariectomy and/or tubectomy	53 (18.9)	47 (41-51)	3	29 (14.9)	49 (43-52)	21	25 (10.4)	47 (40-50)	21
Males		N = 174			N = 152			N = 132	
Thyroidectomy	34 (19.5)	43 (32-51)	16	23 (15.1)	44 (33-51)	17	17 (12.9)	51 (43-54)	31

^a Surgeries are presented when they occurred before a site-relevant cancer could develop. Surgeries in the incident cohort are counted when the surgery was performed after the moment of genetic diagnosis.; IQR = interquartile range

Supplementary table 5. Cancer risks per sex in prevalent cases in the cohort including ca-index patients ^a

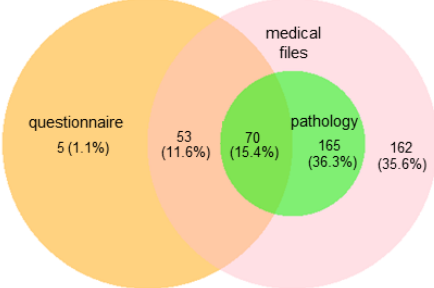
	Prevalent cases in cohort including ca-index patients			
	Cumulative risk		Standardized incidence ratio	
	Age	risk (95%CI)	Age category	ratio (95%CI)
Total				
Any cancer	20	2.4 (1.4 to 4.3)	-	-
	30	10.5 (7.9 to 14.0)	20-29	-
	40	28.2 (23.8 to 33.3)	30-39	-
	50	53.0 (47.0 to 59.3)	40-49	-
	60	69.3 (62.6 to 75.9)	50-59	-
	70	81.6 (72.9 to 88.9)	60-69	-
	-	-	20-69	-
PHTS-related cancer	20	1.8 (0.9 to 3.5)	-	-
	30	8.4 (6.1 to 11.6)	20-29	-
	40	25.5 (21.2 to 30.5)	30-39	-
	50	50.6 (44.4 to 57.0)	40-49	-
	60	65.5 (58.6 to 72.4)	50-59	-
	70	74.8 (66.0 to 82.8)	60-69	-
	-	-	20-69	-
Thyroid cancer	20	1.3 (0.6 to 3.0)	-	-
	30	3.4 (2.0 to 5.7)	20-29	91.4 (41.7 to 173.5)
	40	7.5 (5.1 to 10.9)	30-39	62.1 (29.7 to 114.2)
	50	12.6 (9.1 to 17.5)	40-49	85.9 (42.8 to 153.7)
	60	15.2 (10.9 to 20.8)	50-59	66.5 (17.9 to 170.1)
	70	24.1 (15.8 to 35.8)	60-69	98.3 (19.8 to 287.2)
	-	-	20-69	77.4 (54.5 to 106.6)
Colorectal cancer	20	0.0 (0.0 to 0.0)	-	-
	30	0.3 (0.0 to 1.9)	20-29	27.7 (0.4 to 154.4)
	40	0.9 (0.3 to 2.8)	30-39	13.3 (1.5 to 48.1)
	50	2.6 (1.2 to 5.5)	40-49	10.3 (2.8 to 26.5)
	60	6.4 (3.3 to 12.1)	50-59	5.6 (1.5 to 14.3)
	70	11.7 (6.2 to 21.4)	60-69	4.4 (0.9 to 13.0)
	-	-	20-69	7.1 (3.9 to 12.0)
Colorectal cancer or adenom. polyps ^b	20	0.0 (0.0 to 0.0)	-	-
	30	0.7 (0.2 to 2.3)	20-29	-
	40	4.8 (3.0 to 7.8)	30-39	-
	50	18.0 (13.6 to 23.5)	40-49	-
	60	32.3 (25.5 to 40.2)	50-59	-
	70	53.6 (42.7 to 65.4)	60-69	-
	-	-	20-69	-
Renal cancer	20	0.0 (0.0 to 0.0)	-	-
	30	0.3 (0.0 to 1.8)	20-29	70.7 (0.9 to 393.4)
	40	0.8 (0.3 to 2.6)	30-39	41.7 (4.7 to 150.6)
	50	1.4 (0.5 to 4.0)	40-49	8.0 (0.1 to 44.4)
	60	4.2 (1.8 to 9.4)	50-59	16.9 (3.4 to 49.5)
	70	5.8 (2.6 to 12.6)	60-69	7.5 (0.1 to 41.7)
	-	-	20-69	16.1 (6.9 to 31.7)
Melanoma	20	0.2 (0.0 to 1.6)	-	-
	30	1.5 (0.7 to 3.4)	20-29	18.7 (6.0 to 43.6)
	40	3.1 (1.7 to 5.5)	30-39	12.6 (4.6 to 27.5)
	50	4.5 (2.6 to 7.6)	40-49	3.8 (0.4 to 13.5)
	60	6.4 (3.7 to 11.2)	50-59	7.8 (1.6 to 22.8)
	70	8.1 (4.5 to 14.3)	60-69	5.0 (0.1 to 27.9)
	-	-	20-69	9.1 (5.3 to 14.6)
Female				
Any cancer	20	2.8 (1.4 to 5.6)	-	-
	30	12.0 (8.6 to 16.6)	20-29	-
	40	36.8 (30.8 to 43.5)	30-39	-
	50	69.7 (62.5 to 76.7)	40-49	-
	60	84.8 (78.0 to 90.4)	50-59	-
	70	94.4 (85.9 to 98.6)	60-69	-
	-	-	20-69	-
PHTS-related cancer	20	1.8 (0.7 to 4.2)	-	-
	30	10.6 (7.4 to 15.1)	20-29	-
	40	34.7 (28.8 to 41.4)	30-39	-
	50	68.3 (60.9 to 75.4)	40-49	-
	60	83.8 (76.7 to 89.6)	50-59	-
	70	94.0 (85.0 to 98.5)	60-69	-
	-	-	20-69	-

Breast cancer (including in situ carcinoma)	20	0.0 (0.0 to 0.0)	-	-
	30	4.1 (2.2 to 7.6)	20-29	58.6 (25.2 to 115.4)
	40	25.7 (20.3 to 32.3)	30-39	38.9 (27.8 to 5200.0)
	50	54.4 (46.8 to 62.5)	40-49	24.6 (17.9 to 33.1)
	60	70.4 (62.2 to 78.2)	50-59	17.0 (10.3 to 26.2)
	70	73.4 (64.9 to 81.2)	60-69	3.8 (0.4 to 13.6)
	-	-	20-69	24.4 (20.2 to 29.4)
Breast in situ carcinoma only	20	0.0 (0.0 to 0.0)	-	-
	30	1.6 (0.6 to 4.2)	20-29	-
	40	12.9 (9.0 to 18.5)	30-39	-
	50	24.6 (18.5 to 32.3)	40-49	-
	60	34.0 (25.5 to 44.4)	50-59	-
	70	34.0 (25.5 to 44.4)	60-69	-
	-	-	20-69	-
Endometrial cancer	20	0.0 (0.0 to 0.0)	-	-
	30	1.2 (0.4 to 3.6)	20-29	908.8 (182.7 to 2655.5)
	40	2.8 (1.2 to 6.2)	30-39	41.6 (0.5 to 231.3)
	50	12.0 (7.6 to 18.8)	40-49	150.8 (80.2 to 258.0)
	60	18.9 (12.0 to 29.1)	50-59	14.5 (2.9 to 42.4)
	70	28.3 (16.2 to 46.7)	60-69	30.7 (8.3 to 78.6)
	-	-	20-69	53.2 (34.1 to 79.2)
Thyroid cancer	20	1.4 (0.5 to 3.8)	-	-
	30	4.3 (2.4 to 7.6)	20-29	83.5 (33.5 to 172.1)
	40	8.6 (5.5 to 13.3)	30-39	43.6 (15.9 to 94.9)
	50	14.5 (9.8 to 21.2)	40-49	75.3 (32.4 to 148.3)
	60	15.8 (10.7 to 23.0)	50-59	43.1 (4.8 to 155.7)
	70	30.2 (18.1 to 47.6)	60-69	121.5 (24.4 to 355.1)
	-	-	20-69	65.2 (42.6 to 95.5)
Male				
Any cancer	20	1.8 (0.6 to 5.4)	-	-
	30	8.0 (4.6 to 13.8)	20-29	-
	40	13.1 (8.4 to 20.1)	30-39	-
	50	20.8 (14.3 to 29.6)	40-49	-
	60	36.6 (25.8 to 50.1)	50-59	-
	70	53.8 (36.4 to 73.2)	60-69	-
	-	-	20-69	-
PHTS-related cancer	20	1.8 (0.6 to 5.4)	-	-
	30	4.6 (2.2 to 9.5)	20-29	-
	40	9.0 (5.2 to 15.5)	30-39	-
	50	15.8 (10.1 to 24.3)	40-49	-
	60	26.1 (16.6 to 39.5)	50-59	-
	70	31.8 (19.4 to 49.3)	60-69	-
	-	-	20-69	-
Thyroid cancer	20	1.2 (0.3 to 4.6)	-	-
	30	1.9 (0.6 to 5.7)	20-29	136.3 (15.3 to 492.2)
	40	5.6 (2.7 to 11.6)	30-39	171.0 (46.0 to 437.9)
	50	9.5 (5.1 to 17.4)	40-49	137.6 (27.7 to 402.0)
	60	14.2 (7.7 to 25.1)	50-59	144.7 (16.3 to 522.4)
	70	14.2 (7.7 to 25.1)	60-69	0.0 (0.0 to 0.0)
	-	-	20-69	138.3 (69.0 to 247.5)

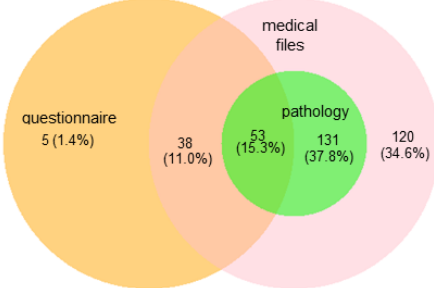
^a - = not assessed.; 95%CI = 95% confidence interval; ^b adenom. polyps = adenomatous polyps

Supplementary Figures

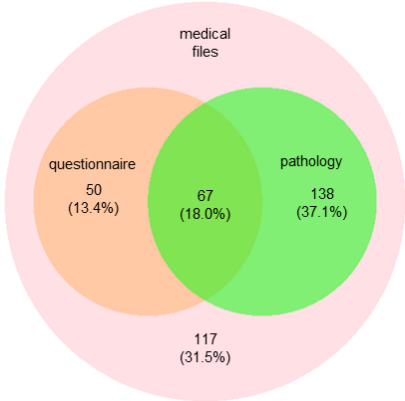
A)



B)



C)



Supplementary figure 1. Schematic overview of data sources available for the cohorts in different analyses. An overview of the number of patients and corresponding percentages (%) with information from different sources for data from medical files (pink), patient questionnaires (orange) and the Dutch nationwide pathology databank (green) for the cohorts prevalent including ca-index patients (A), prevalent excluding ca-index patients (B) and incident including ca-index patients (C).