Supplementary Information

Supplementary Ta	able 1. Stuc	ly names, detail	s, and partic	ipant informa	tion obtained	from the O	ncoArray project ^{1,2} .
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	Study Informa	tion			Partic	cipants		Onco# A	Array Ge Ancestry*	netic				
Abbreviation	Name	Location	Design	Controls	Any PCa	Aggressive PCa	Died of PCa	European	Asian	African	Known PCa Family History	PHS2 (median, IQR)	Age at PCa Diagnosis (median, IQR)	Age at Last Follow-up (median, IQR)
Aarhus (n=1630)	Aarhus Prostate Cancer Study	Aarhus, Denmark	Hospital- based, observational	550	1080	839	65	1621	9	0	856	0.4892 [0.2875, 0.7081]	64.1 [59.8, 68.0]	67.1 [62.3, 71.9]
AHS (n=1650)	Agricultural Health Study	Maryland, USA	Case-control (nested) within prospective cohort	1159	491	238	23	1650	0	0%	1572	0.4193 [0.2232, 0.6236]	67.6 [61.8, 73.5]	75.0 [69.0, 81.2]
ATBC (n=3117)	Alpha-Tocopherol Beta-Carotene	Maryland, USA	Prospective, nested case- control	1910	1207	252	238	3117	0	0	2761	0.4649 [0.2686, 0.6628]	72.0 [69.0, 76.0]	78.6 [74.0, 82.6]
BioVU (n=204)	Vanderbilt University Biorepository	Nashville, USA	Hospital- based, case- control	0	204	0	0	0	0	204	0	0.4768 [0.2658, 0.6174]	61.0 [55.4, 66.5]	61.0 [55.4, 66.5]
Canary PASS (n=373)	Prostate Active Surveillance Study	USA	Prospective, observational	0	373	0	0	364	9	0	0	0.5186 [0.3357, 0.7402]	63.0 [58.0, 67.0]	63.0 [58.0, 67.0]
CCI (n=270)	CCI Prostate	Alberta, Canada	Hospital- based, case series	0	270	71	1	266	4	0	0	0.5666 [0.381, 0.7521]	64.3 [59.1, 68.7]	69.8 [64.7, 75.5]
CeRePP (n=1755)	French Prostate Case Control Study	Paris, France	Case-control, prospective, hospital-based	730	1025	805	13	1567	3	185	1748	0.4935 [0.2943, 0.6984]	66.0 [60.0, 71.0]	68.0 [61.0, 73.0]
CHIPGECS (n=1070)	Chinese Prostate Cancer Genetic and Environmental Correlation Study	China	Population- based, case- control, observational	596	474	293	0	0	1070	0	0	0.3456 [0.1343, 0.5244]	71.0 [65.0, 76.0]	70.0 [63.0, 75.0]
COH (n=519)	City of Hope	Duarte, USA	Case-control	259	260	192	0	516	3	0	260	0.496 [0.2931, 0.7019]	62.0 [55.0, 65.0]	61.0 [56.0, 66.1]
COSM (n=3282)	Cohort of Swedish Men	Stockholm, Sweden	Population- based cohort	1117	2165	1404	278	3279	3	0	2455	0.4861 [0.2975, 0.6946]	69.9 [64.6, 76.5]	78.0 [72.3, 84.1]

CPCS1 (n=791)	Copenhagen Prostate Cancer Study 1	Copenhagen, Denmark	Case-control	256	535	433	8	790	1	0	0	0.4833 [0.2922, 0.692]	68.1 [63.9, 72.6]	70.4 [64.6, 76.2]
CPCS2 (n=667)	Copenhagen Prostate Cancer Study 2	Copenhagen, Denmark	Case-control	227	440	323	3	667	0	0	0	0.483 [0.284, 0.6848]	64.4 [60.7, 67.7]	67.8 [61.0, 71.7]
CPDR (n=176)	Center for Prostate Disease Research	USA	Retrospective	41	135	38	0	0	0	176	153	0.4088 [0.2264, 0.5656]	56.0 [50.7, 62.1]	57.7 [52.7, 65.0]
EPIC (n=1328)	European Prospective Investigation Into Cancer and Nutrition (BPC3)	European Union	Case-control	696	632	180	28	1324	4	0	0	0.4668 [0.2676, 0.6722]	67.2 [62.7, 71.0]	70.3 [65.2, 73.7]
EPICAP (n=29)	EPIdemiologcal study of Prostate CAncer	Hérault, France	Population- based, case- control	9	20	15	3	0	0	29	18	0.47315 [0.2626, 0.583]	64.6 [61.8, 68.6]	64.9 [61.5, 68.5]
ERSPC (n=137)	Erasmus Medical Centre	Rotterdam, The Netherlands	Population- based, randomized control trial	66	71	0	0	136	1	0	0	0.4597 [0.2111, 0.6343]	71.0 [69.5, 73.2]	71.1 [69.5, 73.1]
ESTHER (n=17)	Epidemiological investigations of the chances of preventing, recognizing early and optimally treating chronic diseases in an elderly population	Heidelberg, Germany	Population- based, prospective, case-control	3	14	6	0	17	0	0	17	0.4385 [0.183, 0.5686]	66.6 [64.8, 67.8]	70.8 [67.8, 73.1]
FHCRC (n=812)	Fred Hutchinson Cancer Research Centre	Seattle, USA	Population- based, case control	399	413	226	28	795	17	0	812	0.4739 [0.2901, 0.6608]	60. [55.0, 66.0]	68.0 [60.0, 75.4]
Gene-PARE (n=253)	Genetic Predictors of Adverse Radiotherapy Effects	New York, USA and Tokyo/Chiba, Japan	Hospital-based	0	253	125	0	242	11	0	0	0.56415 [0.3733, 0.73184]	66.3 [61.3, 71.8]	75.3 [69.1, 79.8]
Hamburg-Zagreb (n=295)	Hamburg-Zagreb	Hamburg, Germany	Hospital- based, prospective	149	146	112	10	295	0	0	267	0.4992 [0.2738, 0.6679]	68.3 [62.3, 74.0]	62.0 [54.0, 73.4]

HPFS (n=2221)	Health Professionals Follow-up Study	Boston, USA	Nested case- control	1050	1171	581	75	2212	9	0	368	0.4676 [0.2646, 0.6534]	70.0 [65.0, 75.0]	79.7 [73.7, 84.7]
IMPACT (n=925)	Identification of Men with a genetic predisposition to ProstAte Cancer	The ICR, London, UK	Observational	875	50	24	0	915	10	0	925	0.433 [0.2271, 0.6234]	64.3 [61.0, 67.3]	57.3 [49.9, 64.7]
IPO-Porto (n=551)	Portuguese Oncology Institute	Porto, Portugal	Hospital-based	180	371	276	1	551	0	0	371	0.547 [0.3052, 0.7734]	55.0 [52.0, 61.0]	60.0 [54.0, 65.4]
KARUPROSTATE (n=749)	French West Indies Prostate Cancer Study	French West Indies	Case-control	386	363	226	0	0	0	749	735	0.3629 [0.2113, 0.5466]	66.7 [61.0, 72.0]	63.5 [57.3, 70.2]
KULEUVEN (n=269)	Katholieke Universiteit Leuven	Leuven, Belgium	Hospital- based, prospective, observational	103	166	149	8	269	0	0	40	0.4419 [0.2169, 0.6643]	66.9 [60.4, 71.0]	74.3 [68.5, 80.2]
LAAPC (n=732)	Los Angeles Study of Aggressive Prostate Cancer	California, USA	Population- based, case control	285	447	0	0	720	12	0	0	0.4691 [0.274, 0.6769]	67.0 [60.0, 74.0]	66.0 [58.0, 73.0]
Malaysia (n=405)	Malaysia	Malaysia	Case-control	202	203	175	18	1	404	0	392	0.4113 [0.2112, 0.6088]	70.5 [65.4, 75.5]	75.2 [71.1, 79.5]
MCC-Spain (n=922)	Multi Case-Control Study-Spain	Barcelona, Spain	Case-control	399	523	356	7	917	5	0	879	0.5136 [0.3101, 0.7001]	66.7 [61.7, 72.2]	70.3 [64.5, 76.0]
MCCS (n=1033)	Melbourne Collaborative Cohort Study	Melbourne, Australia	Nested case- control	315	718	374	81	1030	3	0	134	0.5062 [0.2991, 0.7209]	69.2 [65.0, 74.4]	79.2 [73.9, 84.0]
MDACC_AS (n=535)	MD Anderson Cancer Center Active Surveillance Trial	Texas, USA	Prospective, cohort	0	535	151	0	501	34	0	534	0.5305 [0.3522, 0.7361]	64.9 [58.6, 70.3]	64.9 [58.6, 70.3]
MEC (n=1298)	Multiethnic Cohort Study	California / Hawaii, USA	Population- based	670	628	0	29	1240	58	0	1231	0.4677 [0.2608, 0.6595]	69.8 [64.2, 75.3]	79.5 [73.4, 84.7]
MIAMI-WFPCS (n=108)	Miami-Wake Forest Prostate Cancer Study	North Carolina, USA	Case-control	49	59	25	0	0	0	108	107	0.3724 [0.2112, 0.5631]	60.4 [54.8, 65.0]	58.1 [53.0, 64.4]
MOFFITT (n=797)	Moffitt Prostate Cancer Study	Florida, USA	Hospital-based	296	501	268	4	596	9	192	794	0.4863 [0.2998, 0.677]	64.0 [58.7, 69.4]	64.1 [57.3, 71.3]
NMHS (n=364)	Nashville Men's Health Study	Nashville, USA	Clinic-based, case-control	188	176	95	0	0	0	364	364	0.4022 [0.2099, 0.5637]	64.0 [57.0, 69.0]	63.0 [57.0, 68.0]

Oslo (n=1453)	Oslo University Hospital / General Cohort of Adults in Norway (CONOR)	Oslo, Norway	Population- based, observational	0	1453	51	764	1443	10	0	0	0.5692 [0.3692, 0.7409]	72.9 [66.5, 78.4]	79.2 [73.0, 84.3]
PCaP (n=967)	North Carolina- Louisiana Prostate Cancer Project	North Carolina / Louisiana, USA	Population- based cohort	0	967	432	0	0	0	967	967	0.4407 [0.2784, 0.601]	62.0 [56.0, 68.0]	62.0 [56.0, 68.0]
PCMUS (n=281)	Prostate Cancer Study Medical University Sofia	Sofia, Bulgaria	Case-control	89	192	171	0	281	0	0	252	0.4976 [0.3215, 0.7323]	68.0 [63.0, 74.0]	67.9 [62.0, 74.0]
PHS (n=898)	Physicians Health Study	Harvard, Boston, USA	Nested case- control	267	631	375	115	878	20	0	70	0.4947 [0.2983, 0.7133]	68.5 [63.5, 73.5]	82.7 [77.8, 87.3]
PLCO (n=1657)	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Bethesda, USA	Nested case- control	980	677	389	8	1657	0	0	1629	0.4371 [0.253, 0.6419]	72.0 [68.0, 76.0]	74.0 [70.0, 78.0]
Poland (n=801)	The Poland Group	Szczecin, Poland	Case-control	317	484	373	0	800	1	0	437	0.5143 [0.3311, 0.7036]	69.0 [63.0, 76.0]	67.9 [61.0, 74.9]
PRAGGA (n=232)	Prostate cAncer Genetics in Galicia	Galicia, Spain	Case-control	102	130	88	6	229	3	0	204	0.4896 [0.3285, 0.7238]	68.9 [64.6, 72.3]	73.2 [62.8, 78.8]
PROCAP (n=868)	PROgression in Cancer of the Prostate	Stockholm, Sweden	Population- based, observational	241	627	310	215	862	6	0	0	0.5326 [0.317, 0.739]	65.3 [61.3, 68.5]	74.9 [69.2, 79.2]
PROFILE (n=35)	Genetic prostate cancer risk stratification for targeted screening	The ICR, London, UK	Hospital- based, observational, prospective	22	13	7	0	34	1	0	35	0.4871 [0.2868, 0.6777]	61.1 [53.7, 66.8]	57.1 [48.6, 63.0]
PROGReSS (n=996)	Prostate cancer: Mechanisms of Progression and Treatment	Santiago de Compostela, Spain	Hospital- based, observational, prospective	322	674	465	21	995	1	0	174	0.5012 [0.3041, 0.6955]	71.0 [64.7, 75.1]	74.2 [65.5, 79.2]
ProMPT (n=798)	Prostate Cancer: Mechanisms of Progression and Treatment	Cambridge, UK	Population- based	12	786	627	37	791	7	0	156	0.5924 [0.4041, 0.809]	64.5 [60.0, 69.2]	68.2 [63.6, 73.6]

ProtecT (n=1419)	Prostate Testing for Cancer and Treatment	Oxford, Bristol, and Cambridge, UK	Population- based cohort	1415	4	0	0	1413	6	0	1242	0.4101 [0.1987, 0.5984]	64.1 [60.7, 67.9]	61.4 [57.2, 65.4]
PROtEuS (n=123)	The Prostate Cancer and Environment Study	Montreal, Canada	Population- based, case- control	53	70	45	0	0	0	123	118	0.4057 [0.2222, 0.572]	63.5 [57.2, 66.5]	63.9 [59.4, 68.6]
QLD (n=4564)	Queensland Study	Brisbane, Australia	Case-control	1252	3312	2680	53	4504	60	0	2165	0.526 [0.3248, 0.7249]	62.7 [57.8, 67.2]	66.1 [60.4, 71.5]
RAPPER (n=2117)	Radiogenomics: Assessment of Polymorphisms for Predicting the Effects of Radiotherapy	Manchester, UK	Hospital- based, prospective	0	2117	0	0	2100	17	0	0	0.573 [0.3838, 0.7748]	70.6 [66.0, 74.7]	70.6 [66.0, 74.7]
SABOR (n=211)	San Antonio Center of Biomarkers of Risk for Prostate Cancer	San Antonio, USA	Population- based cohort	106	105	37	0	0	0	211	0	0.4537 [0.2669, 0.6288]	63.3 [55.8, 70.2]	63.6 [55.9, 70.4]
SCCS (n=1789)	Southern Community Cohort Study	Southeastern USA	Population- based cohort	1498	291	20	0	0	0	1789	1665	0.3858 [0.2208, 0.5602]	58.0 [53.0, 64.0]	60.0 [53.0, 67.0]
SCPCS (n=89)	South Carolina Prostate Cancer Study	South Carolina, USA	Population- based, case control, observational	32	57	26	0	0	0	89	89	0.4141 [0.2064, 0.5879]	71.0 [68.0, 75.0]	70.0 [67.0, 74.0]
SEARCH (n=2669)	Study of Epidemiology and Risk factors in Cancer Heredity	Cambridge, UK	Case-control	232	2437	1549	148	2637	32	0	1519	0.5569 [0.3672, 0.76]	64.0 [61.0, 67.0]	70.8 [66.6, 74.0]
SFPCS (n=602)	San Francisco Prostate Cancer Study	California, USA	Population- based, case control, observational	241	361	55	50	484	1	117	602	0.4776 [0.2926, 0.6781]	65.0 [58.6, 71.0]	69.1 [62.6, 76.0]
SNP_Prostate_Ghent (n=451)	SNP Prostate Ghent	Ghent, Belgium	Hospital- based, observational	135	316	243	1	451	0	0	393	0.5033 [0.2725, 0.7168]	65.4 [60.6, 70.3]	68.8 [62.8, 75.0]

SPAG (n=211)	Serum Proteomic analysis for biomarkers of Aggressive prostate disease in the Guernsey population	Manchester / Southampton, UK	Hospital- based, observational	172	39	30	1	210	1	0	10	0.4637 [0.2589, 0.658]	66.1 [62.1, 68.5]	68.6 [62.8, 74.4]
STHM2 (n=4524)	Stockholm 2	Stockholm, Sweden	Population- based, observational	1491	3033	1562	96	4497	27	0	0	0.5051 [0.3035, 0.6941]	65.6 [60.9, 70.1]	69.7 [64.6, 74.5]
SWOG-PCPT (n=2409)	Prostate Cancer Prevention Trial	Seattle, USA	Case-control from randomized trial	1273	1136	338	0	2154	91	164	2409	0.4246 [0.2374, 0.6161]	69.0 [65.0, 74.0]	74.4 [70.0, 79.8]
SWOG-SELECT (n=3849)	Selenium and Vitamin E Cancer Prevention Trial	Seattle, USA	Case-control from randomized trial	2307	1542	561	10	3541	111	197	3848	0.4448 [0.2441, 0.6349]	67.0 [63.0, 71.0]	67.0 [62.0, 73.0]
TAMPERE (n=3591)	Finnish Genetic Predisposition to Prostate Cancer Study	Tampere, Finland	Population- based, case- control, observational	1179	2412	1478	146	3585	6	0	134	0.5107 [0.3098, 0.7065]	67.1 [62.8, 71.3]	73.6 [69.5, 78.0]
TORONTO (n=1276)	Toronto	Toronto, Canada	Prospective, hospital-based cohort	544	732	411	0	1123	153	0	1166	0.4956 [0.2958, 0.6852]	65.0 [60.2, 70.6]	63.8 [58.3, 69.3]
UKGPCS (n=11021)	U.K. Genetic Prostate Cancer Study and The Prostate Cancer Research Foundation Study	United Kingdom	Hospital-based	2973	8048	5107	1378	10514	142	365	7772	0.5358 [0.3319, 0.7445]	58.7 [55.2, 63.6]	66.0 [61.7, 73.0]
ULM (n=408)	Institut fuer Humangengetik Ulm	Ulm, Germany	Case-control	3	405	307	13	407	1	0	408	0.5654 [0.3859, 0.7537]	65.0 [60.0, 70.3]	68.6 [63.1, 74.0]
WUGS (n=898)	Washington University Genetics Study	St. Louis, USA	Case series, hospital-based	152	746	430	0	668	6	224	773	0.5091 [0.3173, 0.7336]	62.0 [56.0, 67.0]	64.0 [57.0, 69.0]
Overall (n=80491)				30575	49916	26419	3983	71856	2382	6253	46030	0.4908 [0.2910, 0.6908]	65.3 [59.6, 71.0]	70.0 [63.4, 76.5]

* Genetic ancestry definitions shown here were previously defined using a principal components analysis in OncoArray.

Explorations of Genetic Ancestry

A comparison of self-reported race/ethnicity and OncoArray-defined genetic ancestry^{2,3} is shown in Supplementary Table 2. The performance of PHS was also evaluated using participants' self-reported race/ethnicity. Based on prior power analyses, subgroups with $\geq 1,000$ men were analyzed⁴: European; Black or African American; and East Asian. Those with other/unknown self-reported race/ethnicity were excluded. Model performance was assessed with HR_{80/20}.

Self-reported	Numbor	OncoAr	ray Genetic A	Ancestry
Race/Ethnicity	Number	European	Asian	African
European	63,954	63,685	250	19
Black or African American*	6,247	29	16	6,202
East Asian	1,212	21	1,190	1
Hawaiian	154	138	16	0
Hispanic American	326	139	176	11
South Asian	167	17	150	0
Other/Unknown	8,431	7,827	584	20

Supplementary Table 2. Self-reported race/ethnicity and OncoArray-defined genetic ancestry for individuals in the dataset (n=80,491).

*Includes African American, Black African, Black Caribbean

We also evaluated genetic ancestry and admixture using fastSTRUCTURE⁵, generating agnostic clusters of the data into K=2-6 populations. Supplementary Table 3 shows a comparison of fastSTRUCTURE clustering, OncoArray-defined genetic ancestry, and self-reported race/ethnicity.

Supplementary Table 3. Comparison of fastSTRUCTURE genetic clustering against OncoArray-defined genetic ancestry, and self-reported race/ethnicity for individuals in the dataset (n=80,491).

		OncoArra	y-defined Ancestry	I Genotypic y Self-reported Race/Ethnicity								
		European	Asian	African		European	East Asian	Black or African American	Hawaiian	Hispanic American	South Asian	Other/ Unknown
fastSTRUCTURE K	Cluster	-										
	1	71572	44	0		63514	19	27	136	110	17	7793
K=?	2	0	0	4515		1	0	4507	0	0	0	7
11 L	Admixed	284	2338	1738		439	1193	1713	18	216	150	631
		-0.	2000	1,00		.03	1170	1,10	10	-10	100	001
	1	19959	238	3		17923	6	10	44	91	54	2072
<i>K</i> 2	2	0	2	5483		1	0	5472	0	2	0	10
K=3	3	42128	96	7		37056	9	21	72	89	21	4963
	Admixed	9769	2046	760		8974	1197	744	38	144	92	1386
		•								•		
	1	0	0	5043		1	0	5034	0	0	0	8
	2	8803	958	21		7971	488	21	21	127	61	1093
<i>K</i> =4	3	24801	160	8		22043	9	20	50	74	45	2728
	4	26459	84	7		23242	8	17	57	57	25	3144
	Admixed	11793	1180	1174		10697	707	1155	26	68	36	1458
												1
	1	22760	79	2		20214	36	12	43	28	7	2501
	2	695	47	4346		622	20	4337	2	3	6	98
<i>K</i> =5	3	25057	435	13		22251	227	27	48	91	24	2837
A J	4	4223	400	1397		3771	194	1386	15	29	27	598
	5	8899	757	144		7910	418	143	23	85	46	1175
	Admixed	10222	664	351		9186	317	342	23	90	57	1222

	1	428	284	5095	406	199	5087	4	2	4	105
	2	3401	305	42	3193	58	47	8	76	30	336
	3	7724	258	372	6776	38	364	25	97	66	988
<i>K</i> =6	4	12466	70	255	11170	20	255	19	28	10	1289
	5	16748	9	9	14658	3	12	35	14	3	2041
	6	14789	81	64	13130	8	71	36	36	13	1640
	Admixed	16300	1375	416	14621	886	411	27	73	41	2032

Supplementary Methods

Adapting the PHS to OncoArray: Proxy SNP Identification

To identify proxy single-nucleotide polymorphisms (SNPs) for those not directly genotyped on OncoArray, we identified samples from 12,107 men of European genetic ancestry that were genotyped on both the iCOGs array and OncoArray, within the PRACTICAL consortium. We searched for proxy SNPs (on the same chromosome as the original SNP and within 10⁶ base pairs of the original SNP) with linkage disequilibrium $r^2 \ge 0.90$. Since a suitable proxy could not be identified on OncoArray for all 30 missing SNPs, we re-calculated the β parameter estimates for a Cox proportional hazards regression, using the same dataset used for the initial development of PHS₁. That development dataset includes 18,868 prostate cancer cases and 12,879 controls and has been described previously⁶.

PHS percentile thresholds

Percentiles of PHS₂ were determined from the original reference dataset for PHS₁ (i.e., controls in the development set with age <70 years⁶). Percentiles for PHS₂ are shown in Supplementary Table 4.

Supplementary Table 4. Percentile thresholds of PHS₂.

Percentile	PHS ₂
20 th	0.1603
50 th	0.3949
80 th	0.6521
98 th	0.9966

Sample-Weight Correction and Sensitivity Analysis

In order to appropriately calculate the sample-weight corrections, we needed prostate cancer age-specific incidence rates at a population level. We were able to obtain such information for the following countries: the USA⁷, Sweden^{8–11}, Norway^{8,9}, Finland^{8,9}, Denmark^{8,9}, the UK¹², and Australia¹³. While the incidence rates in each age range varied between countries (likely a reflection of screening prevalence and differing policies for prostate cancer screening in each population), the pattern was relatively similar, and typically varied by a factor of less than 2-3 for each 5-year age bin. Sweden was chosen as a representative population with published raw numbers of men diagnosed with prostate cancer^{10,11} and of total men in the age range of 45-79 years. Published Swedish Cancer Registry and Swedish population data reported there were 9,024 prostate cancer cases and 1,953,203 men without prostate cancer aged 45-79 in 2016^{10,11}. We used these numbers to correct for sampling bias^{14,15} for all Cox proportional hazards regressions reported; calculations were made using the R "survival" package¹⁶.

Given that the overall incidence of prostate cancer in different populations varies, and the current dataset comes from a multi-institutional and multi-national dataset, we performed a sensitivity analysis for the above population numbers. This was done by adjusting the assumed population prostate cancer incidence by a factor of up to four times lesser or greater than that of Sweden, then recalculating the corrected hazard ratios (HRs) for PHS associations with PCa. The range of incidence in the sensitivity analyses (25% to 400% of the Swedish incidence) is wider than the range across the countries mentioned above and wider than the range reported for ethnicity-related variation^{17,18}. We calculated each HR of interest (HR_{20/50}, HR_{80/50}, HR_{98/50}, and HR_{80/20}), for the association of PHS with any PCa, aggressive PCa, and death from PCa (in the multi-ethnic dataset and by each genetic ancestry group, where applicable) to determine how changes in assumed population incidence affected the calculated HRs.

SNPs included in PHS₂

ID	Chromosome	Effect	Reference	Position	PHS ₂ beta
rs6545977	2	А	G	63301164	-0.069
rs1010 †	2	G	А	85808982	-0.049
rs16860513	2	Т	А	173342367	-0.198
rs75219487	3	Т	А	87147922	0.123
rs6788616	3	G	А	87205079	0.041
rs4857841 †	3	А	G	128046643	0.031
rs78416326	3	G	С	170074517	-0.080
rs6853490	4	G	А	95544718	0.053
rs17021918 §	4	А	G	95562877	-0.026
rs7679673 §	4	А	С	106061534	-0.071
rs7725218	5	А	G	1282414	-0.078
rs2736108	5	А	G	1297488	0.056
rs10866527	5	А	G	1891800	0.045
rs3910736	6	А	G	153412476	-0.073
rs7769879	6	С	G	160865645	0.053
rs6965016 †	7	С	А	97807882	0.049
rs11782388 †	8	G	А	23525358	0.062
rs9297746	8	G	А	127909361	-0.061
rs28556804	8	G	А	128014315	-0.074
rs77541621	8	А	G	128077146	0.200
rs1016343	8	А	G	128093297	0.073
rs60163266	8	А	G	128323157	0.073
rs6983267 §	8	А	С	128413305	-0.100
rs7812894 †	8	Т	А	128520479	0.084
rs12549761	8	G	С	128540776	-0.065
rs10993994 §	10	А	G	51549496	0.106
rs72853963	11	А	G	2224664	0.071
rs12275055	11	G	А	68981359	0.083
rs7929962 †	11	G	А	68985583	-0.047
rs11568818 §	11	G	А	102401661	-0.047
rs10875943 §	12	G	А	49676010	0.036
rs55914512	12	А	С	53282274	0.050
rs4643253	14	G	А	69106108	-0.049
rs684232 §	17	G	А	618965	0.042
rs718961	17	А	G	36077099	-0.074
rs11651052 †	17	А	G	36102381	-0.094
rs117576373	17	А	G	46820676	0.138
rs9889335 †	17	А	С	69115146	0.082
rs11672691 §	19	А	G	41985587	-0.062
rs17632542	19	G	А	51361757	-0.160

Supplementary Table 5. SNP identifier, chromosome, effect allele, reference allele, and position (based on version 37) and beta (model weight) for the 46 SNPs used in PHS₂ calculation*.

rs35897249	20	G	А	62233638 -0.049
rs73179053	22	G	А	43501620 -0.081
rs747745	22	G	А	43503547 -0.047
rs4907775 †	23	G	А	51263200 0.056
rs7888856	23	G	А	66751555 -0.047
rs11795627	23	А	G	69957441 -0.040

* Comparing the 46 SNPs included in PHS₂ and the 147 SNPs identified in a recent meta-analysis of men with European ancestry¹, there were 8 PHS₂ SNPs that were exact matches (§) and 9 PHS₂ SNPs in linkage disequilibrium (> 0.90, among men with European ancestry in the present study) (†) with one of the 147 meta-analysis SNPs.

Supplementary Table 6: Summary statistics for PHS₂.

	OncoArray-defined Genetic Ancestry			
PHS ₂ Summary	All	European	Asian	African
Statistics				
Median PHS ₂ (IQR)	0.49 (0.29, 0.69)	0.50 (0.30, 0.70)	0.41 (0.21, 0.60)	0.41 (0.24, 0.57)
Median PHS ₂ (IQR) in <u>controls</u>	0.39 (0.20, 0.58)	0.40 (0.21, 0.59)	0.34 (0.14, 0.52)	0.37 (0.20, 0.54)
Median PHS ₂ (IQR) in participants diagnosed with <u>any</u> prostate cancer	0.55 (0.36, 0.75)	0.56 (0.37, 0.76)	0.47 (0.27, 0.68)	0.43 (0.27, 0.60)
Median PHS ₂ (IQR) in participants diagnosed with <u>aggressive</u> prostate cancer	0.55 (0.36, 0.75)	0.56 (0.37, 0.76)	0.46 (0.25, 0.67)	0.42 (0.27, 0.59)
Median PHS ₂ (IQR) in participants who <u>died</u> of prostate cancer	0.56 (0.37, 0.76)	0.56 (0.37, 0.75)	0.51 (0.28, 0.74)	0.44 (0.31, 0.53)
Median PHS ₂ (IQR) in participants who did not die of prostate cancer	0.49 (0.29, 0.69)	0.50 (0.30, 0.70)	0.40 (0.21, 0.59)	0.41 (0.24, 0.57)

Sensitivity Analyses

Supplementary Table 7: Results of the sensitivity analysis for PHS association with prostate cancer in the multi-ethnic dataset, and by genetic ancestry group. Results are the maximum deviation in each hazard ratio (HR) when the assumed population incidence was varied over a range of values, from 25% to 400% of that reported in Sweden. Each HR was within 2.5% of those reported in the manuscript, even with a 4-fold change (lesser or greater) in the assumed population incidence.

	Maximum deviation of HRs comparing percentiles of PHS ₂				
OncoArray Genetic ancestry	HR _{20/50} : ≤20 th vs 30-70 th	HR _{80/50} : \geq 80 th vs 30-70 th	HR _{98/50} : \geq 98 th vs 30-70 th	HR _{80/20} : $\geq 80^{\text{th}} \text{ vs} \leq 20^{\text{th}}$	
	Any prostate cancer				
All (n=80,491)	1.1%	1.2%	1.9%	2.2%	
European (n=71,856)	1.0%	1.1%	1.8%	2.0%	
Asian (n=2,382)	1.2%	1.3%	2.1%	2.5%	
African (n=6,253)	1.2%	1.1%	2.0%	2.2%	
	Aggressive prostate cancer				
All (n=58,600)	1.1%	1.2%	1.9%	2.2%	
European (n=53,608)	1.0%	1.1%	1.7%	2.0%	
Asian (n=1,806)	1.1%	1.2%	2.0%	2.3%	
African (n=3,186)	1.1%	1.1%	1.9%	2.2%	
	Fatal prostate cancer				
All (n=78,221)	1.8%	1.9%	3.2%	3.7%	

PHS and Family History: Age at Diagnosis of Aggressive Prostate Cancer

Supplementary Table 8: Multivariable models with both PHS and family history of prostate cancer (≥ 1 first-degree relative affected) for association with aggressive and fatal prostate cancer in the multiethnic dataset. Only individuals with known family history were included in these models. Both family history and PHS were significantly associated with aggressive prostate cancer and prostate cancer death in the combined models. Hazard ratios (HR) for family history were calculated as the exponent of the beta from the multivariable Cox proportional hazards regression¹⁹. The HR for PHS in the multivariable models was estimated as the HR_{80/20} (men in the highest 20% vs. those in the lowest 20% of genetic risk by PHS₂) in each cohort. P-values reported are two-tailed from the Cox models. The models with PHS for association with aggressive (log-likelihood $p<10^{-300}$) and fatal (log-likelihood $p=7.8\times10^{-59}$) prostate cancer performed better than the models with family history alone.

OncoArray Genetic Ancestry	Variable	beta	z- score	p-value	HR
	Aggressive Prostate Cancer				
All (n=25.952)	PHS	2.16	47.8	<10-300	5.12
All (n=35,852)	Family History	0.93	31.4	2.0 x 10 ⁻²¹⁶	2.54
			-		
$E_{110000000} (n - 22.010)$	PHS	2.10	46.7	<10-300	4.93
European (n=52,019)	Family History	0.92	31.4	2.0 x 10 ⁻²¹⁶	2.52
			-		
Asian (n=902)	PHS	1.73	38.9	10-300	3.60
	Family History	0.33	6.7	2.1 x 10 ⁻¹¹	1.39
African (n-2.021)	PHS	1.10	22.1	3.2 x 10 ⁻¹⁰⁸	2.16
African (n=2,931)	Family History	0.94	31.5	8.7 x 10 ⁻²¹⁸	2.57
	Fatal Prostate Cancer				
All (n=46,030)	PHS	2.20	16.3	9.9 x 10 ⁻⁶⁰	5.29
	Family History	0.78	8.5	1.9 x 10 ⁻¹⁷	2.18

Explorations of Alternative Ancestry Groupings

Self-reported race/ethnicity

Supplementary Table 9: Association of PHS with aggressive prostate cancer, by self-reported race/ethnicity. Hazard ratios (HRs) are shown comparing men in highest 20% of genetic risk ($\geq 80^{\text{th}}$ percentile) vs. the lowest 20% of genetic risk ($\leq 20^{\text{th}}$ percentile).

Self-reported Race/Ethnicity	HR _{80/20} : ≥80th vs ≤20th		
European	5.52 [5.48, 5.57]		
Black or African American	2.40 [2.36, 2.44]		
East Asian	2.85 [2.74, 2.98]		

fastSTRUCTURE

Supplementary Table 10. Association of PHS with aggressive prostate cancer, by K=2-6 clusters using fastSTRUCTURE. Hazard ratios (HRs) are shown comparing men in highest 20% of genetic risk ($\geq 80^{\text{th}}$ percentile) vs. the lowest 20% of genetic risk ($\leq 20^{\text{th}}$ percentile).

fastSTRUCTURE K	Cluster	HR _{80/20} : ≥80th vs ≤20th	
	1	5.60 [5.55, 5.64]	
<i>K</i> =2	2	2.06 [2.03, 2.09]	
	Admixed	5.05 [4.89, 5.21]	
	1	5.75 [5.66, 5.83]	
<i>V</i> -2	2	2.43 [2.39, 2.47]	
K-3	3	5.42 [5.37, 5.47]	
	Admixed	6.37 [6.25, 6.50]	
	1	2.17 [2.13, 2.20]	
	2	5.28 [5.19, 5.40]	
<i>K</i> =4	3	5.75 [5.68, 5.83]	
	4	5.56 [5.49, 5.63]	
	Admixed	6.07 [5.97, 6.19]	
	1	6.06 [5.97, 6.14]	
<i>K</i> =5	2	6.31 [6.09, 6.54]	
	3	6.09 [6.01, 6.29]	

	4	6.11 [5.94, 6.29]
	5	5.09 [5.00, 5.20]
	Admixed	4.85 [4.76, 4.94]
	1	5.32 [5.14, 5.49]
	2	6.41 [6.19, 6.66]
	3	4.76 [4.67, 4.87]
<i>K</i> =6	4	6.62 [6.50, 6.75]
	5	5.18 [5.10, 5.26]
	6	5.57 [5.47, 5.66]
	Admixed	5.91 [5.83, 6.01]

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References from Supplemental Material

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