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Supplemental information

Polygenic risk for prostate cancer: Decreasing relative risk with age but little impact on absolute risk

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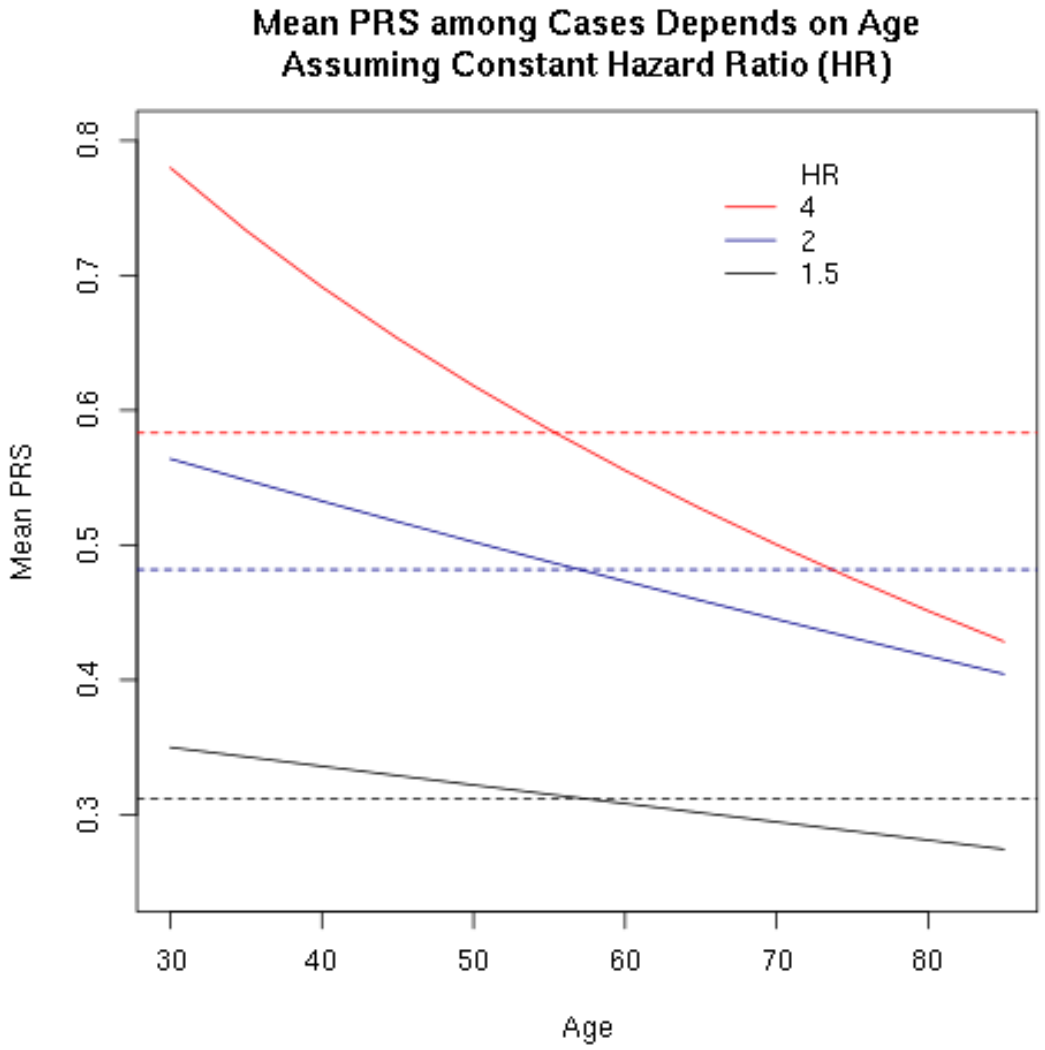
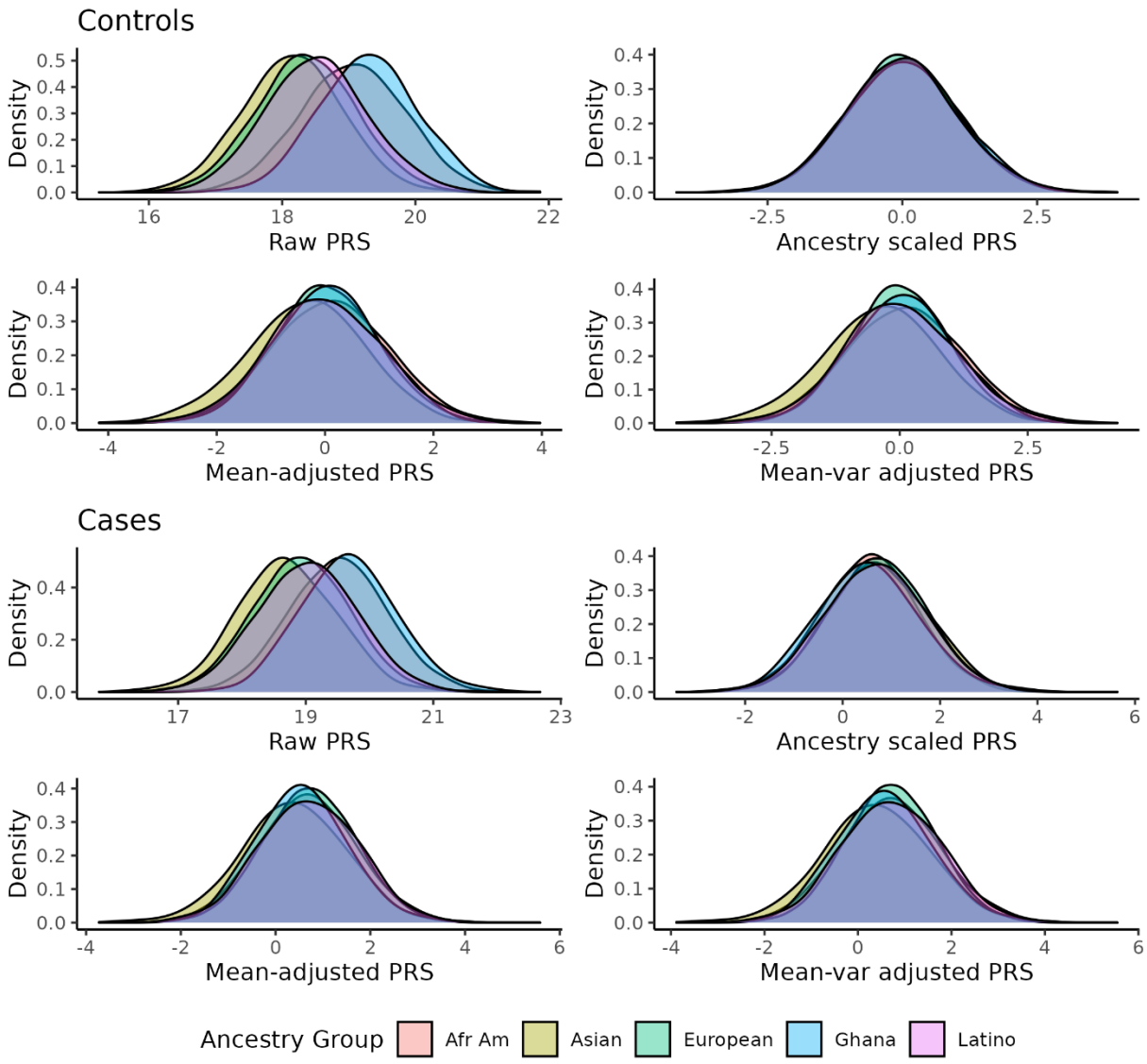
Supplemental Information

Figure S1.



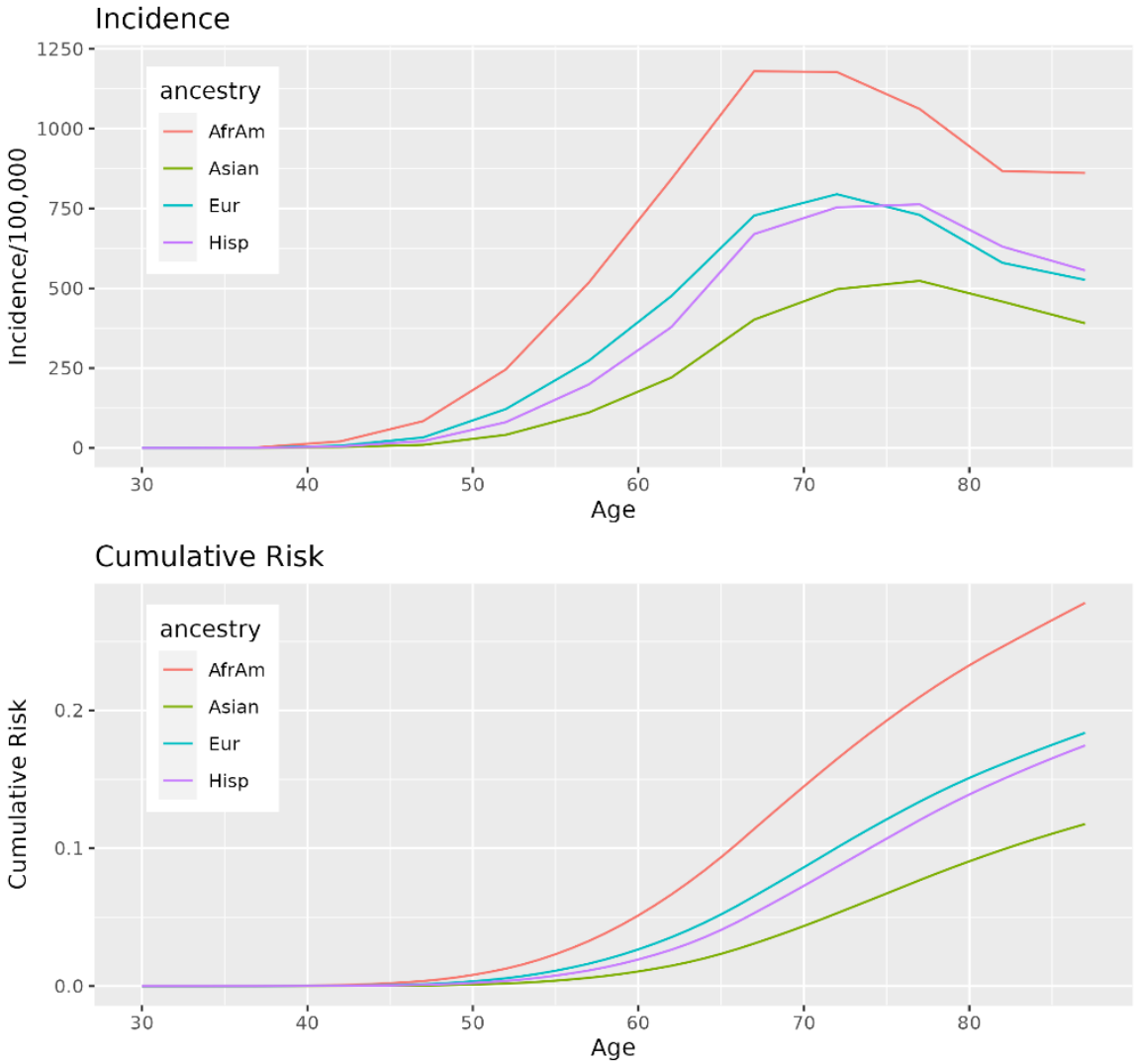
Mean PRS among cases over different ages, assuming a constant hazard ratio. The solid lines illustrate how the mean PRS is expected to decrease with age, and the horizontal dashed lines provide perspective on how the solid lines pivot from a constant value. See Methods section for Theoretical Mean PRS Among Cases & Age for derivations used to create Figure S1.

Figure S2



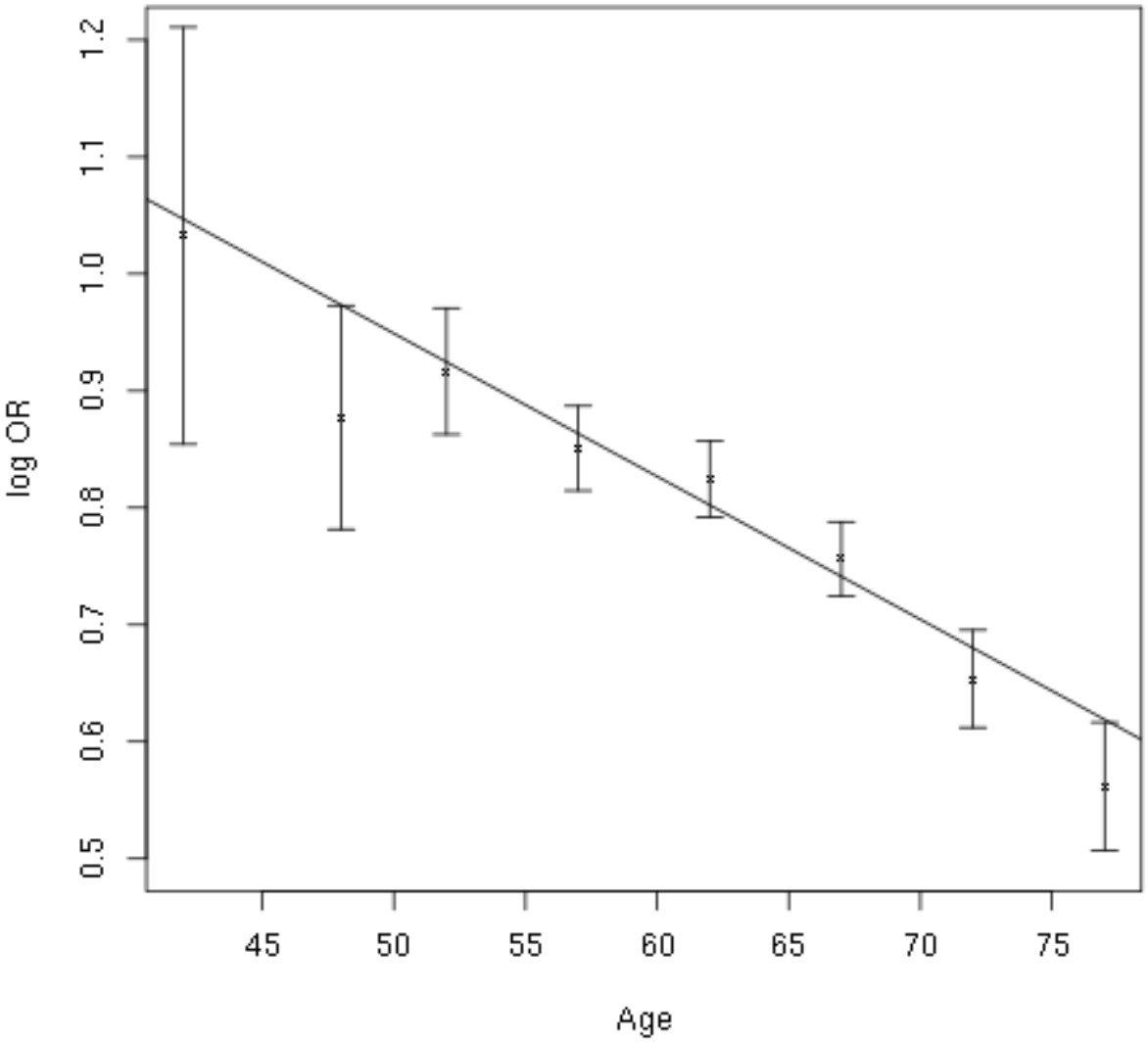
Distribution of PRS uncorrected (raw PRS) and corrected by various methods for controls and cases. See Methods section PRS Ancestry Correction by Projection onto 1,0000 Genome Reference Sample for details.

Figure S3.



Age-specific incidence of prostate cancer, per 100,000, for different ancestry groups (upper panel) and corresponding cumulative risk of prostate cancer (lower panel). See Methods section Age-Specific Incidence and Cumulative Risk by Ancestry for details.

Figure S4.



Piece-wise log-odds-ratios ("*" and their 95% confidence intervals represented as whiskers) and model assuming log-odds-ratio depends linearly on age (solid line). The piece-wise results are positioned on the x-axis at the median value of age within each age group. See Methods section on Linear Decrease in PRS Log-Odds-Ratio with Age for details.

Table S1. Studies obtained from dbGaP for Prostate Cancer Genome Wide Association Study Data. See Methods section Description of dbGaP Studies for more details

dbGaP Study Accession		Study Label	Study Full Name
phs000207.v1.p1		CGEMS	CGEMS Prostate Cancer GWAS - Stage 1 – PLCO (Embargo Release Date: December 22, 2009)
phs000306.v4.p1		GENEVA	GENEVA Prostate Cancer (Embargo Release Date: February 01, 2013)
phs000812.v1.p1		BPC3	Characterizing Genetic Susceptibility to Breast and Prostate Cancer - BPC3 (Embargo Release Date: June 11, 2015)
phs000838.v1.p1		GHANA	Ghana Prostate Study (Embargo Release Date: July 10, 2015)
phs000882.v1.p1		PEGASUS	National Cancer Institute (NCI) Prostate Cancer Genome-wide Association Study for Uncommon Susceptibility Loci (PEGASUS) (Embargo Release Date: January 24, 2017)
phs001391.v1.p1		ONCO	OncoArray: Prostate Cancer (Embargo Release Date: March 21, 2018)
phs000733.v1.p1		ICPCG	The International Consortium for Prostate Cancer Genetics Genome Wide Association Study of Familial Prostate Cancer (Embargo Release Date: March 10, 2015)

Table S2. Sample Size before and after quality control, merging, and removal of related subjects.

Study	Downloaded Data		After Initial QC (1)		After Merging and Removing Related Subjects (2)	
	Cases	Controls	Cases	Controls	Cases	Controls
BPC3	2782	4458	2775	4451	2179	3573
CGEMS	1151	1101	1140	1097	520	414
GENEVA	4304	4529	4264	4496	4115	4371
ICPCG	2568	1422	2520	1392	2106	1022
ONCO	52700	37751	52658	37723	51489	36910
PEGASUS	4599	2841	4595	2840	3670	2290
GHANA	474	458	474	458	461	452
Total	68578	52560	68426	52457	64540	49032

(1) Reasons for exclusion include low call rate (<80%), low heterozygosity (<0.4) on any chromosome, self-reported sex inconsistent with chromosome X and Y data.

(2) One subject was randomly removed from each related pair (kinship coefficient ≥ 0.0442)

Table S3: Exclusions by study.

	BPC3 (N=5752)	CGEMS (N=934)	GENEVA (N=8486)	ICPCG (N=3128)	ONCO (N=88399)	PEGASUS (N=5960)	WAFR (N=913)	Total (N=113572)
Missing Age	0	0	0	123	2677	0	0	2800
Age < 30	0	0	0	0	39	0	0	39
Missing Ancestry	0	0	0	27	0	0	0	27

Table S4. Description of studies included in analyses [a]

	BPC3 (No.=5752)	CGEMS (No.=934)	GENEVA (No.=8486)	ICPCG (No.=2978)	ONCO (No.=85683)	PEGASUS (No.=5960)	WAFR (No.=913)	Total (No.=110706)
Status								
Case	2179 (37.9%)	520 (55.7%)	4115 (48.5%)	2072 (69.6%)	51257 (59.8%)	3670 (61.6%)	461 (50.5%)	64274 (58.1%)
Control	3573 (62.1%)	414 (44.3%)	4371 (51.5%)	906 (30.4%)	34426 (40.2%)	2290 (38.4%)	452 (49.5%)	46432 (41.9%)
Ancestry								
Afr.Amer	0	0	4521 (53.3%)	0	6354 (7.4%)	0	0	10875 (9.8%)
Asian	0	0	1935 (22.8%)	0	1122 (1.3%)	0	0	3057 (2.8%)
European	5752 (100.0%)	934 (100.0%)	0	2978 (100.0%)	75999 (88.7%)	5960 (100.0%)	0	91623 (82.8%)
Ghana	0	0	0	0	0	0	913 (100.0%)	913 (0.8%)
Latino	0	0	2030 (23.9%)	0	2208 (2.6%)	0	0	4238 (3.8%)
Family History PrCa								
Unknown	1483	0	3024	0	29730	5960	913	41110
No	3826 (89.6%)	844 (90.4%)	4923 (90.1%)	906 (30.4%)	45896 (82.0%)	0	0	56395 (81.0%)
Yes	443 (10.4%)	90 (9.6%)	539 (9.9%)	2072 (69.6%)	10057 (18.0%)	0	0	13201 (19.0%)
Age Group								
[30,45)	0	0	77 (0.9%)	79 (2.7%)	1163 (1.4%)	0	2 (0.2%)	1321 (1.2%)
[45,50)	22 (0.4%)	0	206 (2.4%)	210 (7.1%)	2557 (3.0%)	0	2 (0.2%)	2997 (2.7%)
[50,55)	86 (1.5%)	0	444 (5.2%)	448 (15.0%)	8121 (9.5%)	0	134 (14.7%)	9233 (8.3%)
[55,60)	339 (5.9%)	121 (13.0%)	905 (10.7%)	628 (21.1%)	16423 (19.2%)	300 (5.0%)	146 (16.0%)	18862 (17.0%)
[60,65)	929 (16.2%)	0	1296 (15.3%)	620 (20.8%)	19219 (22.4%)	1212 (20.3%)	150 (16.4%)	23426 (21.2%)
[65,70)	1669 (29.0%)	497 (53.2%)	1816 (21.4%)	562 (18.9%)	18923 (22.1%)	1768 (29.7%)	169 (18.5%)	25404 (22.9%)
[70,75)	1413 (24.6%)	0	1796 (21.2%)	257 (8.6%)	11651 (13.6%)	1674 (28.1%)	175 (19.2%)	16966 (15.3%)
[75,88)	1294 (22.5%)	316 (33.8%)	1946 (22.9%)	174 (5.8%)	7626 (8.9%)	1006 (16.9%)	135 (14.8%)	12497 (11.3%)
Age,median (range)	69 (45,87)	67 (57, 77)	67 (44, 77)	61 (33, 87)	63 (30, 87)	67 (57, 77)	65 (42, 87)	64 (30, 87)

[a]Excluding men with missing age, age < 30 years, or missing ancestry

Table S5. Self-reported ancestry versus ancestry based on the maximum estimate of admixture probability. See Methods section Ancestry: Self—Reported and Genetically Informed for more details.

Genetic Admixture Max Probability	Self-reported Ancestry				
	African American	Asian	European	Latino	Ghana
African	10354	1	0	11	913
Amerindian	7	113	0	1637	0
Asian	33	2746	7	24	0
European	481	197	88638	2566	0

Table S6. Intercept and slope for models of log-risk of PRS as a function of age in years.

Model	Intercept (SE)	Slope (SE)
Weighted Cox	1.2504 (0.049)	-0.0138 (0.0015)
Logistic Regression	1.1935 (0.035)	-0.0122 (0.0010)

Table S7. Log-relative risk estimates (beta) and their standard errors (se) for Figure 2.

Ancestry	beta_persd	se_persd	beta_up90	se_up90
Afr Amer	0.7054	0.0309	1.3904	0.0681
Ghana	0.5132	0.0834	1.0916	0.2031
Latino	0.6858	0.0433	1.1945	0.1038
Asian	0.7743	0.0654	1.4182	0.1377
European	0.7666	0.0140	1.3720	0.0326

Table S8. Log-relative risk estimates (beta) and their standard errors (se) for Figure 3.

Ancestry	Age	beta_persd	se_persd	beta_up90	se_up90
Afr Am	[30, 55)	0.7867	0.0403	1.4177	0.0831
Afr Am	[55, 60)	0.7188	0.0408	1.3718	0.0888
Afr Am	[60, 65)	0.6699	0.0417	1.3081	0.0937
Afr Am	[65, 70)	0.7160	0.0473	1.4152	0.1084
Afr Am	[70, 88)	0.6454	0.0593	1.4397	0.1570
Ghana	[30, 55)	0.7179	0.1838	1.1702	0.4502
Ghana	[55, 60)	0.6935	0.1604	1.6039	0.4118
Ghana	[60, 65)	0.7092	0.1485	1.6726	0.3498
Ghana	[65, 70)	0.5790	0.1562	0.9123	0.4200
Ghana	[70, 88)	0.3404	0.0963	0.8264	0.2365
Latino	[30, 55)	0.7937	0.0848	1.4939	0.1839
Latino	[55, 60)	0.8194	0.0774	1.4036	0.1577
Latino	[60, 65)	0.7615	0.0622	1.2271	0.1374
Latino	[65, 70)	0.6782	0.0614	1.2064	0.1367
Latino	[70, 88)	0.5812	0.0651	1.0218	0.1673
Asian	[30, 55)	0.8122	0.1175	1.4138	0.2478
Asian	[55, 60)	0.7960	0.1041	1.5453	0.2087
Asian	[60, 65)	0.9118	0.1006	1.6689	0.1861
Asian	[65, 70)	0.8676	0.0942	1.4500	0.1744
Asian	[70, 88)	0.6744	0.0933	1.2949	0.2177
Eur	[30, 55)	0.9384	0.0177	1.6969	0.0332
Eur	[55, 60)	0.8715	0.0156	1.5575	0.0304
Eur	[60, 65)	0.8081	0.0157	1.4314	0.0326
Eur	[65, 70)	0.7178	0.0183	1.2914	0.0403
Eur	[70, 88)	0.6227	0.0296	1.1045	0.0784

Table S9. Tests of heterogeneity of relative risks across ages for parameters in Table S8.

	Test of Heterogeneity of Relative Risk across Ages	
Ancestry	Per SD PRS	Upper 90th Percentile of PRS
Afr Am	0.221	0.902
Ghana	0.112	0.228
Latino	0.099	0.321
Asian	0.473	0.746
Eur	0.000	0.000

Table S10. Log-relative risk estimates (beta) and their standard errors (se) for Figure 5.

FamHx	Age	beta_perSD	se_perSD
No	[30, 55)	0.8922	0.0236
No	[55, 60)	0.8427	0.0204
No	[60, 65)	0.7824	0.0221
No	[65, 70)	0.6713	0.0230
No	[70, 88)	0.6141	0.0382
Yes	[30, 55)	0.9803	0.0459
Yes	[55, 60)	0.9366	0.0464
Yes	[60, 65)	0.8072	0.0526
Yes	[65, 70)	0.7777	0.0617
Yes	[70, 88)	0.7432	0.1107

Methods

Theoretical Mean PRS Among Cases & Age

The mean PRS among cases depends on the strength of association of the PRS with disease and it is possible for the mean PRS to be greater among younger cases than older cases, even if the hazard ratio associated with a PRS is constant over all ages. This is because men who have greater values of PRS are at the greatest susceptibility for disease and are more likely to succumb at a younger age.

Below we derive the expected PRS among cases, and how this expectation depends on age, when assuming a constant hazard ratio (e.g., proportional hazards model). The derivation follows standard methods for survival analyses. Assume that the standardized PRS, z, has a standard normal density, $\phi(z)$. The probability of disease at age a, conditional on z, is

$P(a \mid z) = \lambda_o(a) e^{\beta z} S_o(a)^{\exp(\beta z)}$, where $\lambda_o(a)$ is the baseline hazard rate, $S_o(a) = \exp[-\sum_{t=0}^{a} \lambda_o(t)]$, and β is the log hazard ratio constant over age. From these, we determine the density of z conditional on disease at age a:

$$P(z \mid a) = \frac{\lambda_o(a) e^{\beta z} S_o(a)^{\exp(\beta z)} \phi(z)}{\int_{-\infty}^{\infty} \lambda_o(a) e^{\beta z} S_o(a)^{\exp(\beta z)} \phi(z) \partial z}. \quad (1)$$

The expected value of z among diseased cases at age a is then

$$E[z \mid a] = \int_{-\infty}^{\infty} zP(z \mid a)dP \qquad (2)$$

To illustrate this numerically, we assume that age of disease diagnosis has an exponential distribution (i.e., constant hazard rate of λ=.003, the mean baseline incidence for European ancestry), and a constant log hazard ratio of β, making it easy to numerically integrate equations (1) and (2). Figure S1 illustrates how the mean PRS among cases decreases with age, while the mean PRS among controls is expected to be approximately zero.

PRS Ancestry Correction by Projection onto 1,0000 Genome Reference Sample

Because the distribution of PRS differs across different ancestries due to SNP allele frequency differences, we evaluated three approaches to correct for population differences: 1) centering and scaling the PRS within each ancestry group, using the mean and standard deviation for controls within each ancestry group; 2) projection of data onto 1,000 Genome reference panel and correction of mean PRS;[1] 3) projection of data onto 1,000 Genome reference panel and correction of both mean PRS and variance of PRS. These latter two methods intend to provide a continuum of correction for men of different ancestries, some admixed.

The projection methods #2 and #3 (Christopher Kachulis, Broad Institute, personal communication), are based on projecting the study sample PRS onto a reference sample. This is accomplished by computing the PRS on the reference sample and using linear regression to regress the reference PRS on the top (maybe 10) principal components of the reference sample. The regression coefficients from this reference regression are used to predict the PRS in the study sample, by using the sample principal components. This predicted value is then subtracted from the sample PRS to adjust for ancestry. Because this approach only corrects for the mean of the distribution, it might not fully correct for ancestry if the variance of the PRS differs across ancestry. To adjust for the variance, one can create residuals from the linear regression in the reference sample, and then perform a second linear regression of the squared residuals on the principal components in the reference sample. This can then be used to predict the variance in the study sample, by using the regression coefficients with the sample principal components. To illustrate, the PRS adjusted score would be computed as

$$PRS_{adjusted} = \frac{PRS_{sample} - (\alpha_o + \sum \alpha_i PC_i)}{\sqrt{\beta_o + \sum \beta_i PC_i}},$$

where α coefficients are estimated by regression of the PRS on the principal components in the reference samples, β coefficients are estimated by regression of the squared residuals on the principal components in the reference samples**,** and PRS_{sample} and PC_i are from the study samples.

When computing the above PRS corrections, the genetic variants need to be available in both the study and reference samples. For the prostate cancer PRS, there were 220 variants available in our study sample, but only 212 of these were available in the 1000 Genome reference (8 variants were in our prostate cancer studies but not available in the 1000 Genome reference data). To compute the principal components, we removed the 212 risk variants and removed variants in linkage disequilibrium, resulting in approximately 100,000 variants.

The panels in Figure S2 below illustrate the distribution of the raw PRS, the PRS corrected by self-reported ancestry mean and standard deviation among controls ("Ancestry scaled PRS"), the PRS corrected by projection on the reference samples, correcting for the mean ("Mean-adjusted PRS"), and the PRS corrected by projection correcting for both mean and variance ("Mean-Var adjusted PRS"). For our prostate cancer study, it can be seen that the projection methods do not fully correct for ancestry, by viewing the non-overlapping distributions among controls. In contrast, the self-reported ancestry mean and standard deviation correction performed better.

Age-Specific Incidence and Cumulative Risk by Ancestry

The age-specific incidence rates of prostate cancer, as described in the main manuscript methods, are illustrated in the upper panel of Figure S3. This figure illustrates the greater incidence rate among African American ancestry across all ages, the lesser incidence among Asian ancestry and similar incidence among European and Latino (Hispanic) ancestries. The incidence rates, λ_t, can be used to compute the cumulative incidence of prostate cancer by age *a*, $F(a) = \exp[-\sum_{t=0}^{a} \lambda_t]$. The cumulative incidences in the ancestral populations are illustrated in the lower panel of Figure S3. By age 87, the life-time risk of prostate cancer is expected to be 28% among African American men, 18% among European ancestry, 17% among Latino ancestry, and 12% among Asian ancestry.

Linear Decrease in PRS Log-Odds-Ratio with Age

The results in the main manuscript, illustrated in Figure 4, were based on fitting Cox proportional hazards models with weights the inverse of population incidence rates for controls. Since men were enrolled based on case-control studies, we evaluated the sensitivity of our conclusions of log-relative-risk decreasing linearly with age among European ancestry by fitting piece-wise logistic regression models for age partitioned into 5 year intervals, from age 30 to age 88. In addition, a logistic regression model assuming linear change in PRS risk according to age was fit by the form of status ~ cohort + (age-30) + PRS + I((age-30)* PRS). The results from piece-wise fits and the linear model are illustrated in Figure S4. The linear decrease in log-odds-ratio fits the data well for ages 50-70. Table S6 below shows that parameter estimates and their standard errors for the weighted Cox model and the logistic regression model are consistent, and quite close for the linear decrease in log risk.

Description of dbGaP Studies

A brief description of each the studies obtained from dbGaP and listed Table S1 is provided below. Complete descriptions are available from the dbGaP web site (https://www.ncbi.nlm.nih.gov/gap/)

CGEMS

The Cancer Genetic Markers of Susceptibility (CGEMS) prostate cancer genome-wide association study (GWAS) included genotyping approximately 550,000 SNPs (Phase 1A with HumanHap300 and Phase 1B HumanHap240, both from Illumina, San Diego, CA) in 1,172 prostate cancer patients and 1,157 controls of European ancestry from the Prostate, Lung, Colon and Ovarian (PLCO) Cancer Screening Trial. Selected publications include:[2]

Acknowledgement**:** Data submitted to dbGaP by Lead Principal Investigator Stephen J. Chanock. Laboratory of Translational Genomics, Division of Cancer Epidemiology and Genetics, National Cancer Institute and Core Genotyping Facility, Division of Cancer Epidemiology and Genetics (DCEG), National Cancer Institute (NCI), National Institutes of Health, Department (NIH), Department of Health and Human Services (DHHS), Bethesda, MD, USA. dbGaP accession phs000207.v1.p1.

GENEVA

This study is part of the Gene Environment Association Studies initiative (GENEVA, http://www.genevastudy.org) funded by the trans-NIH Genes, Environment, and Health Initiative (GEI). The version 1 release of this dataset included genotype data for the Japanese and Latino populations in the study. Genotyping was performed at the Broad Institute of MIT and Harvard, a GENEVA genotyping center and at the University of Southern California. Selected publications include:[3; 4]

Acknowledgement: Funding support for the GENEVA Prostate Cancer study was provided through the National Cancer Institute (R37CA54281, R01CA6364, P01CA33619, U01CA136792, and U01CA98758) and the National Human Genome Research Institute (U01HG004726). Assistance with phenotype harmonization, SNP selection, data cleaning, meta-analyses, data management and dissemination, and general study coordination, was provided by the GENEVA Coordinating Center (U01HG004789-01). dbGaP accession phs000306.v4.p1.

BPC3

The Breast and Prostate Cancer Cohort Consortium (BPC3) was established in 2003 to pool data and biospecimens from nine large prospective cohorts to conduct research on gene-environment interactions in cancer etiology. The BPC3 GWAS includes the following cohorts: the American Cancer Society Cancer Prevention Study-II (CPS-II); the European Prospective Investigation of Cancer (EPIC); the Physician's Health Study (PHS); the Nurses' Health Studies I and II (NHS and NHSII); the Health Professionals Follow-up Study (HPFS); the Multiethnic Cohort (MEC); the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial; and the Alpha-Tocopherol, Beta-Carotene (ATBC) Study. Selected publications include:[5-7]

Acknowledgement: The Breast and Prostate Cancer Cohort Consortium (BPC3) genome-wide association studies of advanced prostate cancer and estrogen-receptor negative breast cancer was supported by the National Cancer Institute under cooperative agreements U01-CA98233, U01-CA98710, U01-CA98216, and U01-CA98758 and the Intramural Research Program of the National Cancer Institute, Division of Cancer Epidemiology and Genetics. dbGaP accession phs000812.v1.p1

GHANA

Participants were recruited through the Ghana Prostate Study (a population-based component and a clinical component) between 2004 and 2006. Additional prostate cancer cases were recruited between 2008 and 2012. Selected publications include:[8-14]

Acknowledgement: The genome-wide association study of prostate cancer in West African men project was supported by the Intramural Research Program of the National Cancer Institute, National Institutes of Health, Department of Health and Human Services including Contract No.

HHSN261200800001E. The datasets have been accessed through the NIH database for Genotypes and Phenotypes (dbGaP). A full list of acknowledgements can be found in the supplementary note [8]. dbGaP accession phs000838.v1.p1

PEGASUS

This genome-wide association study was funded by the National Cancer Institute (NCI) to identify uncommon susceptibility loci for prostate cancer. A total of 7440 subjects of European ancestry from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial were genotyped using the Illumina HumanOmni2.5.

Acknowledgement: The National Cancer Institute (NCI) Prostate Cancer Genome-wide Association Study for Uncommon Susceptibility Loci (PEGASUS) was supported by the Intramural Research Program of the NCI. Please see publication number 14 dbGaP accession phs000882.v1.p1.[15]

ONCO

Original description of the study: From ELLIPSE (linked to the PRACTICAL consortium), ~78,000 SNPs were contributed to the OncoArray. A large fraction of the content was derived from the GWAS meta-analyses in European ancestry populations (overall and aggressive disease; ~27K SNPs). An additional just over 10,000 SNPs were selected from the meta-analyses in the non-European populations, with a majority of these SNPs coming from the analysis of overall prostate cancer in African ancestry populations as well as from the multiethnic meta-analysis. A substantial fraction of SNPs (~28,000) were also selected for fine-mapping of 53 loci not included in the common fine-mapping regions (tagging at r2>0.9 across ±500kb regions). A few thousand SNPs related with PSA levels and/or disease survival as well as SNPs from candidate lists provided by study collaborators, as well as from meta-analyses of exome SNP chip data from the Multiethnic Cohort and UK studies, were also selected. A large number of studies contributed to the total sample (99,622): see description at the web link https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001391.v1.p1.

Acknowledgement: dbGaP accession phs001391.v1.p1. See below for **OncoArray: Prostate Cancer Acknowledgements.**

ICPCG

The aim of this study was to perform a GWAS for prostate cancer cases that came from pedigrees with multiple men affected with prostate cancer. Pedigrees were identified that had 3 or more related prostate cancer cases and have an average age at diagnosis ≤ 75 years. Only one case was chosen from each pedigree; if more than one case was available in a pedigree, the most

aggressive case was chosen, or if no aggressive cases, the case with the earliest age of diagnosis was chosen. Male controls were selected such that they were unrelated to cases and to each other and had a distribution of race and birth year similar to the cases. A GWAS was performed based on genotyping with the Illumina 5M plus exome SNP set. Selected references include:[16-19]

Acknowledgement: Data was provided by principal investigator Lisa Cannon Albright, PhD. The University of Utah, UT, USA, and funding provided by R01 CA089600. National Institutes of Health, Bethesda, MD, USA. The genotyping data was generated and provided by the International Consortium for Prostate Cancer Genetics (ICPCG). The ICPCG was funded by a grant from the National Institutes of Health, U01 CA89600. dbGaP accession phs000733.v1.p1.

Ancestry: Self-Reported and Genetically Informed

The program ADMIXTURE[20] was used to estimate genetic admixture probabilities using a reference sample of 1000 Genome supplemented with data from the Human Genome Diversity Project.[21] We found the ADMIXURE software to provide odd results for very large sample sizes (~100,000), presumably due to numerical accuracy when computing the log-likelihood. For this reason, we partitioned samples into batches of size no greater than 10,000. The results in Table S5 below illustrate that potential misclassification was minimal among subjects self-reported as African American, European and Ghana. Asian subjects had a small number genetically classified as Amerindian, yet there is close ancestry among Amerindian and Asians, so these might represent historical ancestries. Latino ancestry is known to be admixed among Amerindian, European, and African. Note that the classification by maximum genetic admixture probability includes subjects that are bordering 50:50 admixture between two ancestries, such as 51% European and 49% African who self-report as African.

Model to Adjust Weights to Fit Age Distribution Among Cases

To evaluate the sensitivity of the weights in the Cox model, we modified the population incidence (hazard) rates to better fit the age distribution of the cases to allow for the possibility that the cases were sampled with preference to certain ages. Based on theory of survival analysis, the probability density of an event occurring at age t is

$$f(t) = \lambda_t S(t)$$

where λ_t is the population hazard rate and $S(t) = \exp(-\sum_i^t \lambda_t)$, assuming age is partitioned into one year increments. Assuming multiplicative changes to λ_t to adapt our weights to the age of diagnosis among the cases, we modeled the hazards as $\lambda_t e^{\beta_t}$, where β_t are parameters to estimate. The likelihood for the cases is

$$L = \prod_{t=30}^{87} \left(\lambda_t e^{\beta_t} \exp(-\sum_i^t \lambda_t e^{\beta_t}) \right)^{N_t}$$

Where $30 \le t \le 87$ for our cases and N_t is the number of cases at age of diagnosis t. We estimated the β_t parameters by the Newton-Raphson method, and use the revised hazard rates $\lambda_t e^{\beta_t}$ to weight the controls (weight of $1/(\lambda_t e^{\beta_t})$, and used ancestry-specific λ_t and β_t in these computations.

OncoArray: Prostate Cancer
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