Title page

Family history of prostate and breast cancer integrated with a polygenic risk score identifies men at highest risk of dying from prostate cancer before age 75 years

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Running title: Family history of cancer integrated with PRS

Statement of translational relevance

Family history of prostate cancer has traditionally been used for prostate cancer risk stratification. Here we show that family history of prostate and breast cancer integrated with a polygenic risk score can improve risk stratification substantially and identify men at highest risk of dying of prostate cancer before age 75 years. Likewise, men at low risk – approximately 40% of men in the analyzed cohort – can be identified and potentially be spared intensive prostate cancer screening. Our results support integrating a polygenic risk assessment for prostate cancer into clinical practice.

Abstract

Purpose: Family history of prostate cancer is one of the few universally accepted risk factors for prostate cancer. How much an assessment of inherited polygenic risk for prostate cancer adds to lifetime risk stratification beyond family history is unknown.

Experimental Design: We followed 10,120 men in the Health Professionals Follow-up Study with existing genotype data for risk of prostate cancer and prostate cancer-specific death. We assessed to which extent family history of prostate or breast cancer combined with a validated polygenic risk score (PRS) including 269 prostate cancer risk variants identifies men at risk of prostate cancer and prostate cancer death across the age span.

Results: During 20 years of follow-up, 1,915 prostate cancer and 166 fatal prostate cancer events were observed. Men in the top PRS quartile with a family history of prostate or breast cancer had the highest rate of both prostate cancer and prostate cancer-specific death. Compared with men at lowest genetic risk (bottom PRS quartile and no family history), the hazard ratio was 6.95 (95% CI 5.57-8.66) for prostate cancer and 4.84 (95% CI 2.59-9.03) for prostate cancer death. Men in the two upper PRS quartiles (50-100%) or with a family history of prostate or breast cancer (61.8% of the population) accounted for 97.5% of prostate cancer deaths by age 75 years.

Conclusions: Our study shows that prostate cancer risk stratification on the basis of family history and inherited polygenic risk can identify men at highest risk of dying from prostate cancer before age 75 years.

Introduction

Family history of prostate cancer is one of the few universally accepted risk factors for prostate cancer. Clinically, family history has been used for cancer risk stratification and screening recommendations. In the last few years, polygenic risk scores (PRSs) have been shown to outperform family history in predicting prostate cancer risk [1, 2]. While a family history of prostate cancer increases the risk of being diagnosed with prostate cancer by a factor of 1.5 to 2 [3-6], a PRS including 269 single nucleotide polymorphisms (SNPs) showed over a 10-fold increased odds of prostate cancer comparing the top and bottom deciles of genetic risk [1, 7]. This suggests that the PRS is more informative for stratifying men according to their inherited genetic risk – with better identification of both men with high and men with low risk of disease – than family history alone.

Family history may still add a value when assessing genetic risk of prostate cancer [8]. Current PRS do not fully explain the heritability of prostate cancer (around 40% of the familial relative risk is captured by the 269 SNP-PRS [1]) and do not include rare pathogenic germline variants, such as alterations within *BRCA2*, *HOXB13* and *ATM*. While genetic testing for such rare variants has become less expensive and more accessible, they are unlikely to capture all, including yet to be identified, pathogenic variants. Family history partly reflects the presence of rare pathogenic variants, and we previously showed that men with a family history of prostate or breast cancer had an increased risk of overall and lethal prostate cancer [3]. It is currently unknown to which extent a PRS adds to lifetime risk of prostate cancer and prostate cancer death, beyond family history of prostate or breast cancer.

In this study, we integrated information on family history of breast and prostate cancer with the 269-SNP PRS among men in the Health Professionals Follow-up Study (HPFS) with available genotype data. In a secondary analysis, we examined a 313-SNP PRS for breast cancer [9] to further explore potential shared genetic susceptibility. We hypothesized that combining different heritable measures improves lifetime risk stratification for both prostate cancer and prostate cancer-specific death.

Material and Methods

Study population

HPFS is a prospective cohort of 51,529 US male health professional recruited in 1986 at the age of 40-75 years [10]. At baseline and every 2 years, participants were sent questionnaires collecting data on medical history, lifestyle data, and disease outcomes. Information on family history of prostate cancer was collected in 1990, 1992 and 1996, and on family history of breast cancer in 1996. All men in HPFS were invited to provide either a blood (received from 18,159 participants during the period 1993 to 1999) or buccal cell sample (received from 13,956 participants during the period 2005 to 2006). Of these men, 10,917 men have been genotyped as a part of multiple nested case-control studies as described previously [11], including a prostate cancer case-control study of 2,000 cases and controls [12]. The total sample of genotyped men correspond to 53% of men who provided blood and 11% of men who provided buccal cell material (see Statistical analysis how this was handled). In addition to having genotyped data, the inclusion criteria for the present analysis were being alive and prostate cancer-free in 1996 when data on family history of breast cancer was collected, resulting in a final study population of 10,120 men aged 50 years or above at study entry. The vast majority of men (99%) self-reported as White.

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required. All participants gave written informed consent.

Exposure

Genetic risk was defined based on categories of family history of either prostate or breast cancer (yes/no) in a first-degree relative (parent or sibling), and quartiles of the previously validated prostate cancer PRS (264 SNPs were available for analysis) [1]. For more robust age-specific calculations of absolute risks, we used a broader definition of genetic risk based on family history and a PRS above or below the median. A secondary analysis included quartiles of the 313-SNP breast cancer PRS [9]. Genotyping and imputation were performed as previously described [11]. The PRS was calculated by multiplying the log odds ratio [1] with the genotype dosage for each SNP and summed up over all SNPs.

Outcomes

Primary outcomes were prostate cancer and prostate-cancer specific death. Prostate cancer incidence was first identified on biennial questionnaires, and subsequently confirmed through medical and pathology records. Date and cause of death was determined through searches in the National Death Index and reports of next of kin. A physician endpoint committee blinded to exposure data assigned cause of death based on death certificates and medical records. Follow-up of HPFS for cancer incidence (>96%) and mortality (>99%) is high.

Statistical analysis

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Men contributed follow-up-time from the date of their 1996 questionnaire return or the date of DNA collection, if later, to the date of prostate cancer diagnosis or prostate cancer-specific death, death from other causes, or were censored at the end of follow-up in January 2017 (outcome: prostate cancer) or January 2019 (outcome: prostate cancer-specific death), whichever came first.

Cox proportional hazards regression with age as the underlying time scale was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for associations between categories of genetic risk and the two outcomes. Model discrimination was measured by Harrell's Concordance (C) statistic. All models were stratified by 10-year birth cohort and further adjusted for calendar period of DNA collection (1993-1999, 2005-2006) and genetic ancestry (principal components 1-3). Secondary analyses included additional adjustment for the following non-genetic factors potentially contributing to the association between family history and the outcomes: prostate-specific antigen (PSA) screening, history of other cancers, history of diabetes, current aspirin use, current statin use, smoking, body mass index (BMI) and physical activity. To account for possible bias that could arise from the genotype sampling design, HR were estimated from inverse probability weighted (IPW) models aiming at reconstructing the underlying cohort. As previously described [13], each genotyped participant was weighted by the inverse probability of being selected for genotyping.

We further calculated absolute risks of prostate cancer and prostate cancer death using the Aalen-Johansen estimator of the cumulative incidence function [14]. Non-prostate cancer death was treated as a competing event and the cumulative incidence by age 85 years is referred to as lifetime risk. We calculated the proportion of total risk accounted for by men in different categories based on a competing risk models in which events for each category was treated as a separate event. The cumulative incidence for each event was divided by the total cumulative

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incidence by age 70, 75, 80 and 85 years. Based on the cumulative incidence, we also calculated

the age at which men in certain genetic risk categories would reach the same level of risk as an

average man in the study population aged 75 years.

All analyses were performed using R.

Data availability

Data are available through a project proposal for the Health Professionals Follow-up Study

(https://sites.sph.harvard.edu/hpfs/for-collaborators).

Results

A total of 10,120 men were included, with a median age of 65.3 years at study entry (Table 1). Of

the 2,557 (25.3%) men reporting a family history of prostate or breast cancer, 49.9% had a family

history of prostate cancer only, 42.4% a family history of breast cancer only, and 7.7% a family

history of both. Men with a family history of prostate or breast cancer had a higher PRS and a

higher proportion of men reporting a previous PSA test, but were otherwise similar in baseline

characteristics compared to men without a family history.

In total, 1,915 prostate cancer and 166 fatal prostate cancer events were observed during a

median follow-up time of 18.3 (interquartile range (IQR), 11.1 to 22.8) and 23.2 (IQR, 13.8 to

25.0) years, respectively. As previously reported [3], having a family history of cancer was

associated with an increased rate of prostate cancer, with hazard ratios of 1.24 (95% CI 1.06-

1.44) for a family history of breast cancer only, 1.58 (95% CI 1.38-1.81) for a family history of

prostate cancer only and 1.65 (95% CI 1.21-2.24) for a family history of both cancers (Table 2).

The pattern was similar for prostate cancer-specific death. In contrast to family history of breast

cancer, the breast cancer PRS was not associated with an increased rate of prostate cancer or

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prostate cancer-specific death (Supplementary Table 1). Genetic risk measured by the prostate cancer PRS demonstrated a strong association with both outcomes: compared with the bottom PRS quartile, the hazard ratio in the top PRS quartile was 5.29 (95% CI 4.47-6.27) for prostate cancer and 3.68 (95% CI 2.29-5.90) for prostate cancer-specific death (Table 2).

Combining the prostate cancer PRS and family history of prostate or breast cancer yielded the largest gradient in risk. Compared with men at lowest genetic risk (bottom PRS quartile and no family history of prostate or breast cancer), men in the top PRS quartile with a family history of prostate or breast cancer had the highest rate of prostate cancer (HR 6.95; 95% CI 5.57-8.66), followed by men in the top PRS quartile without a family history (HR 4.95; 95% CI 4.06-6.03) (Table 2). The same pattern was observed for prostate cancer-specific death, with hazard ratios of 4.84 (95% CI 2.59-9.03) for men in the top PRS quartile with a family history, and 3.44 (95% CI 1.96-6.03) for men in the top PRS quartile without a family history. Models including a family history of prostate cancer only and models including additional adjustment for PSA screening history, smoking, BMI, diabetes, other cancers and medication use showed similar results (Supplementary Table 2 and Supplementary Table 3).

Model discrimination for prostate cancer, measured by Harrell's C statistic, increased from 0.61 for a model including only family history of prostate cancer to 0.72 for a model including the PRS and family history of prostate cancer, and 0.73 for a model including the PRS and family history of prostate or breast cancer (Supplementary Table 4). Model discrimination for prostate cancer-specific death was stronger than for prostate cancer, with corresponding C-statistics of 0.67 (family history of prostate cancer), 0.77 (PRS and family history of prostate cancer) and 0.77 (PRS and family history of either cancer).

Across PRS categories, the absolute risks of both prostate cancer and prostate cancer-specific death was higher among men with a family history of prostate or breast cancer than among men without a family history (Fig. 1A, Fig. 1B, and Supplementary Table 5). Among men in the top PRS quartile, the lifetime risk of prostate cancer death was 3.2% (95% CI 1.9-5.2) for men with a family history and 1.8% (95% CI 1.2-2.7) for men without a family history. Among men in the bottom PRS category, the corresponding lifetime risk was 1.2% (95% CI 0.5-2.9) for men with a family history and 0.4% (95% CI 0.1-0.8) for men without a family history.

Most events occurred among men in the two upper PRS quartiles (50-100%) or with a family history of prostate or breast cancer (Fig. 2A and Fig. 2B). These men (61.8% of the population) accounted for 100% of prostate cancer-specific deaths by age 70 years, 97.5% of prostate cancer-specific deaths by age 75 years, 94.4% of prostate cancer-specific deaths by age 80 years, and 89.4% of prostate cancer-specific deaths by age 85 years (Table 3). Of the 33 fatal events by age 75 years, 15 (representing 42.3% of the total risk) occurred among men with a PRS above the median but without a family history and 17 (representing 55.2% of the total risk) occurred among men with a family history. Excluding men in the PRS 50-75% category from this definition left out 10 of the 33 prostate cancer deaths by age 75 years and the remaining men (43.0% of the population) accounted for 68.9% of prostate cancer deaths by age 75 years (Supplementary Table 6).

We further examined the age at which a man within a specific genetic risk category reached the same absolute risk level of prostate cancer-specific death as an average man in the study population aged 75 years (Table 4). Men with a family history and a PRS above the median reached the same risk level (0.5%) 15 years earlier, by age 60 years. Men with a PRS below the

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median and no family history were on the opposite end of the spectrum and reached this risk level 12 years later, by age 87 years.

Discussion

Based on data from a large cohort of men prospectively followed for 20 years, this study provides compelling evidence for integrating a prostate cancer PRS with information on family history of prostate and breast cancer in prostate cancer screening and risk assessment. This is particularly relevant for assessing risk of dying from prostate cancer – in this cohort of men, close to 100% of the total risk of prostate cancer-specific death by age 75 years occurred in men with a PRS above the median or with a family history of prostate or breast cancer. Following, men with a PRS below the median and no family history of prostate or breast cancer, approx. 40% of men, had no to low risk of dying from prostate cancer before age 75 years. This group of men also reached the same level of risk 12 years later than the average man. This suggests that men with a low PRS and no family history of cancer need a less intensive prostate cancer screening protocol than men with a high PRS or a positive family history. While screening starting at age 40 years has been recommended for *BRCA2* pathogenic variant carriers, and should be considered for carriers of other DNA repair gene alterations, there are currently no guidelines that incorporate PRS [15]. Incorporating the PRS may both provide an earlier identification of high-risk cancers and reduce the burden associated with over-diagnosis and over-treatment of low-risk cancers.

Our study is the first to provide long-term data on the risk of prostate cancer-specific death using the multiancestry 269-SNP PRS and incorporating information on family history of both breast and prostate cancer. Given the heterogeneous nature of prostate cancer, with many men presenting with indolent cancers, it is important that risk stratification tools capture men at highest risk of dying from the disease. While a few recent studies have examined combinations of

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PRS and family history on prostate cancer risk [6, 16, 17], only two published [2, 18] and one

pre-print [19] study have to our knowledge included prostate cancer death as an outcome. These

studies were based on earlier or different versions of the PRS and had limited follow-up for

prostate cancer death [2, 19] and included family history of prostate cancer only [2, 18, 19].

However, as in our study, including genetic risk scores substantially improved prediction of

prostate cancer death as compared with family history and other risk factors.

Previous research has shown that family history of cancer reflects in part the presence of rare

pathogenic variants. In particular, alterations within *HOXB13*, *BRCA1*, *BRCA2*, and *ATM* have

been reported to be enriched among prostate cancer cases with a family history of prostate,

breast, or ovarian cancer [20-22]. In our study we observed that family history of breast cancer,

but not the breast cancer PRS, was associated with an increased prostate cancer risk. This is in

accordance with a study evaluating shared genetic susceptibility across cancer types, in which no

association between a breast cancer PRS (or any other cancer PRS after taking variants in linkage

disequilibrium into account) and prostate cancer risk was observed [23]. Current PRS do not

generally cover rare germline alterations (because they are not captured by most genotyping

arrays), but family history presumably would to some degree, which could explain our finding.

The advantage of family history is that it can be obtained without genetic testing and that it also

captures environmental disease risks shared across family members and potentially also

epigenetic factors. The drawback of family history is that it is an indirect measure of genetic risk,

which may not always be complete or available. While direct measurements would usually be

preferred, and increasingly feasible with reduced costs for DNA sequencing, there is currently

only a modest overlap between the three measures of genetic risk (family history, PRS, and rare

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pathogenic variants), suggesting that all three are needed to accurately estimate genetic risk [2, 8].

Although we lacked a direct measurement of rare pathogenic variants in the current, our analysis is in agreement with a recent study based on data from the UK Biobank examining the combined effect of rare pathogenic variants and the multiancestry 269-SNP PRS [24]. As in our study, men in the top PRS decile carrying a rare pathogenic variants had the highest lifetime risk of prostate cancer (56%). Our findings also consistent with another study, based on a 147-SNP PRS, reporting the highest lifetime risk of prostate cancer among *BRCA1* or *BRCA2* pathogenic variant carriers with a PRS in the 95th percentile (lifetime risk of 50% and 88%, respectively) [25]. None of these studies had sufficient data to examine prostate cancer-specific death.

In practice, the PRS and family history information – ideally combined with rare pathogenic variants – can be used to narrow down the number of men to be targeted for more intensive screening and evaluation. Approximately 60% of men in the current analysis belonged to the increased genetic risk category (PRS 50-100% or a family history of prostate or breast cancer), where the vast majority of prostate cancer deaths were observed. A more narrow categorization, for example PRS 75-100% or a positive family history, would reduce the percentage of men categorized as being at increased genetic risk, but this would at the same time exclude approximately one third of the early prostate cancer deaths. Integration of the PRS with tools that are specific for clinically-significant disease, such as multiparametric MRI, may be the most promising approach to avoid over-diagnosis of indolent disease while identifying high-risk cancers to a high degree [26]. Further studies are needed to detail out how a prostate cancer screening protocol incorporating the PRS would look like, including the optimal age when to start screening or initiate treatment. Our data suggest that men at high genetic risk may need screening

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starting 15 years earlier than the average man, which based on the guidelines for PSA screening [27-29], would be at around age 40 years, corresponding to the age recommended for *BRCA2* pathogenic variant carriers.

Limitations of this work included not having updated information on family history beyond 1996 and not having data on non-European ancestry groups. The 269-SNP PRS has been developed for and validated in multiancestry populations for prostate cancer, but is currently unknown if findings are generalizable to other ancestry groups. This study leveraged a cohort of men in HPFS for whom genotype data were available and may not be fully representative of the underlying cohort. There is an over-representation of prostate cancer cases in the underlying data due to the genotype sampling design, which influenced absolute risk estimates for overall prostate cancer but not relative risk estimates, which were similar to previous estimates including the full cohort of men [3]. This over-representation also did not affect lifetime risk estimates of prostate cancer death, which were similar to those estimated for U.S. men (2.4%) [30]. However, absolute risk trajectories may be somewhat specific for a health-conscious population – men in HPFS are highly trained health professionals and are generally healthier than men in the general U.S. population who have higher rates of smoking, obesity, and physical inactivity, three factors linked to an increased risk of early prostate cancer death [31]. Despite the large number of prostate cancers included, we did not have enough statistical power for additional subgroup analysis beyond a four-group categorization of the PRS and presence versus absence of family history. We also did not have any midlife PSA measurement, which has previously been shown to predict risk of prostate cancer death [32], and our analysis did not include men under the age of 50 years. Several strengths should be noted. HPFS is a prospective cohort study with extensive data collection (including PSA screening history), long-follow up, and verified disease endpoints.

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Family history of prostate cancer was available from before large-scale implementation of PSA screening, which should be noted as a strength as it likely reflects family history of clinically relevant prostate cancer to a higher degree. The ability to study prostate cancer death is an important feature of this cohort.

In conclusion, our study shows that prostate cancer risk stratification on the basis of family history and inherited polygenic risk can identify men at highest risk dying from prostate cancer at an early age. Additional studies are needed to examine if this improved identification, followed by appropriately tailored treatment, translates to improved survival in the long-term. Nevertheless, there is now robust evidence that incorporation of a PRS provides a better assessment of genetic risk of prostate cancer, and most importantly, prostate cancer death, than a traditional examination of family history alone.

Acknowledgments

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Table 1. Characteristics of genotyped men in the Health Professionals Follow-up Study at start of follow-up (1996 or date of DNA collection, if later).

	All men	Family history of prostate or breast cancer	
		No	Yes
No. of men	10,120	7,563	2,557
Age at start of follow-up, years (median [IQR])	65.3 [58.2, 71.9]	65.3 [58.3, 71.9]	64.8 [57.5, 72.0]
Family history (FH) (%)			
No FH	7563 (74.7)	7563 (100.0)	–
FH of prostate cancer only	1276 (12.6)	–	1276 (49.9)
FH of breast cancer only	1085 (10.7)	–	1085 (42.4)
FH of both cancers	196 (1.9)	–	196 (7.7)
Prostate cancer PRS (median [IQR])	23.8 [23.2, 24.3]	23.7 [23.2, 24.3]	23.8 [23.3, 24.4]
Prostate cancer PRS quartiles			
0-25%	2530 (25.0)	1960 (25.9)	570 (22.3)
25-50%	2530 (25.0)	1905 (25.2)	625 (24.4)
50-75%	2530 (25.0)	1904 (25.2)	626 (24.5)
75-100%	2530 (25.0)	1794 (23.7)	736 (28.8)
PSA test history (%)	8463 (83.6)	6253 (82.7)	2210 (86.4)
Smoking (%)			
Never smoker	4998 (49.4)	3722 (49.2)	1276 (49.9)
Past smoker quit >10 years ago	3909 (38.6)	2935 (38.8)	974 (38.1)
Current or past smoker quit ≤ 10 years ago	1213 (12.0)	906 (12.0)	307 (12.0)
BMI, kg/m^2 (%)			
<25	4023 (39.8)	2989 (39.5)	1034 (40.4)
25 to <30	4786 (47.3)	3598 (47.6)	1188 (46.5)
≥30	1311 (13.0)	976 (12.9)	335 (13.1)
High vigorous physical activity [a] (%)	2486 (24.6)	1849 (24.4)	637 (24.9)
History of diabetes (%)	928 (9.2)	723 (9.6)	205 (8.0)
Current statin use (%)	1496 (14.8)	1157 (15.3)	339 (13.3)
Current aspirin use (%)	5192 (51.3)	3856 (51.0)	1336 (52.2)

Abbreviations: BMI, body mass index; FH, family history; IQR, interquartile range; PSA, prostate specific antigen; PRS, polygenic risk score.
[a] Defined as ≥3 h/week of vigorous activity (activities requiring ≥6 metabolic equivalents) and/or ≥7 h/week of brisk walking.

Table 2. Hazard ratios and 95% confidence intervals for the association of family history of prostate or breast cancer and the prostate cancer polygenic risk score with prostate cancer (1996–2017) and prostate cancer death (1996–2019).

Genetic risk group	Prostate Cancer		Prostate Cancer Death	
	No. of events / PY	HR (95% CI) [a]	No. of events / PY	HR (95% CI) [a]
Family history (FH) of prostate or breast cancer				
No FH	1,301/286,055	1 (Ref.)	110/325,496	1 (Ref.)
Only FH of prostate cancer	333/43,453	1.58 (1.38-1.81)	30/51,199	1.60 (1.06-2.42)
Only FH of breast cancer	230/38,495	1.24 (1.06-1.44)	21/44,283	1.32 (0.82-2.12)
FH of both cancers	51/6,591	1.65 (1.21-2.24)	5/7,712	1.87 (0.76-4.62)
Prostate cancer PRS				
0-25%	180/97,895	1 (Ref.)	23/116,337	1 (Ref.)
25-50%	307/94,694	1.73 (1.43-2.10)	25/112,117	1.11 (0.63-1.95)
50-75%	528/93,205	3.02 (2.53-3.60)	50/104,963	2.35 (1.43-3.86)
75-100%	900/88,801	5.29 (4.47-6.27)	68/95,272	3.68 (2.29-5.90)
Combined genetic risk				
PRS 0-25%				
no FH	134/77,291	1 (Ref.)	17/92,032	1 (Ref.)
+ FH of prostate or breast cancer	46/20,604	1.17 (0.82-1.65)	6/24,306	1.18 (0.46-3.03)
PRS 25-50%				
no FH	217/73,123	1.70 (1.36-2.12)	16/85,442	0.99 (0.50-1.96)
+ FH of prostate or breast cancer	90/21,571	2.10 (1.59-2.78)	9/26,675	1.62 (0.72-3.65)
PRS 50-75%				
no FH	362/70,255	2.82 (2.29-3.47)	33/78,739	2.16 (1.20-3.88)
+ FH of prostate or breast cancer	166/22,950	4.14 (3.25-5.28)	17/26,224	3.31 (1.67-6.53)
PRS 75-100%				
no FH	588/65,386	4.95 (4.06-6.03)	44/69,283	3.44 (1.96-6.03)
+ FH of prostate or breast cancer	312/23,414	6.95 (5.57-8.66)	24/25,989	4.84 (2.59-9.03)

Abbreviations: CI, confidence interval; FH, family history; HR, hazard ratio; PRS, polygenic risk score; PY, person-years; Ref., reference.
[a] Inverse probability-weighted Cox regression models, stratified by 10-year birth cohort and adjusted for age (underlying time-scale), calendar period of DNA collection (1993-1999, 2005-2006), and genetic ancestry (principal components 1-3).

Table 3. Proportion of total risk of prostate cancer and prostate cancer death captured by men with a polygenic risk score above the median or with a family history of prostate or breast cancer up until age 70, 75, 80, and 85 years.

Age	Prostate Cancer		Prostate Cancer Death	
	No. of events / Total No. of events	Proportion of total risk, % [b]	No. of events / Total No. of events	Proportion of total risk, % [b]
Age 70 years				
PRS 50-100% or FH of prostate or breast cancer [a]	729/860	85.9	17/17	100
PRS 0-50% + FH	55/860	6.2	5/17	24.4
PRS 50-100% but no FH	431/860	49.2	6/17	33.9
PRS 50-100% + FH	243/860	30.6	6/17	41.7
Age 75 years				
PRS 50-100% or FH of prostate or breast cancer [a]	1,109/1,316	85.3	32/33	97.5
PRS 0-50% + FH	90/1316	6.5	5/33	15.2
PRS 50-100% but no FH	673/1316	50.1	15/33	42.3
PRS 50-100% + FH	346/1316	28.7	12/33	40.0
Age 80 years				
PRS 50-100% or FH of prostate or breast cancer [a]	1,392/1,680	84.1	60/64	94.4
PRS 0-50% + FH	124/1680	7.0	7/64	11.4
PRS 50-100% but no FH	838/1680	49.3	33/64	49.4
PRS 50-100% + FH	430/1680	27.8	20/64	33.7
Age 85 years				
PRS 50-100% or FH of prostate or breast cancer [a]	1,517/1,845	83.4	89/100	89.4
PRS 0-50% + FH	133/1845	6.9	11/100	11.3
PRS 50-100% but no FH	921/1845	49.4	50/100	48.8
PRS 50-100% + FH	463/1845	27.1	28/100	29.3

Abbreviations: FH, family history; PRS, polygenic risk score.
[a] Represents 61.8% of the study population.
[b] Calculated based on the total cumulative incidence of each outcome by age 70, 75, 80, and 85 years.

Table 4. Age at which 0.5% absolute risk of prostate cancer death was reached, summarized by genetic risk group. A comparison is made against the average man in the study population who reached 0.5% risk by age 75 years.

| Genetic risk group	Age when reaching 0.5% absolute risk of prostate cancer death, years	Difference in age compared with the average man, years
PRS 0-50%		
no FH	87	12
FH	68	-7
PRS 50-100%		
no FH	75	0
+ FH	60	-15

Figure 1. Across PRS categories, absolute risks were highest among men with a family history of prostate or breast cancer. **A,** Absolute risk of prostate cancer by attained age according to family history of prostate or breast cancer and the prostate cancer PRS. **B,** Absolute risk of prostate cancer-specific death by attained age according to family history of prostate or breast cancer and the prostate cancer PRS.

Figure 2. Most events occurred among men in the two upper PRS quartiles (50-100%) or with a family history of prostate or breast cancer. **A,** Illustration of the proportion of total risk of prostate cancer captured by men with a prostate cancer PRS above the median or with a family history of prostate or breast cancer (represented by the blue color). **B,** Illustration of the proportion of total risk of prostate cancer-specific death captured by men with a prostate cancer PRS above the median or with a family history of prostate or breast cancer (represented by the blue color).

Figure 1

A

B
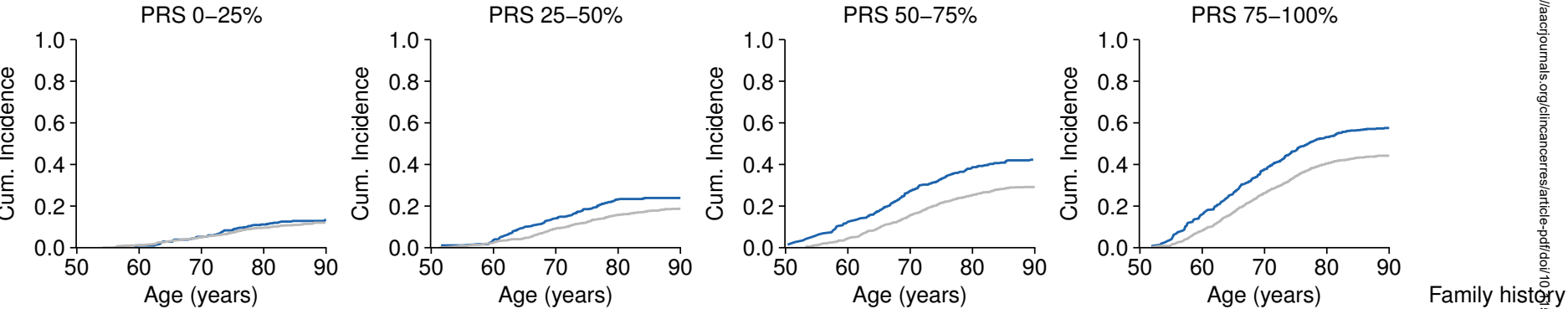
Figure 2

A   Prostate Cancer

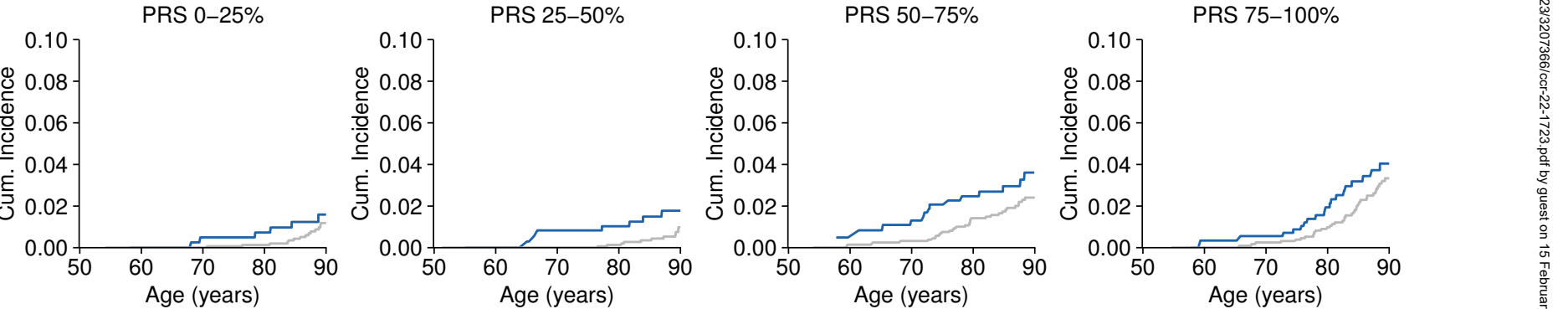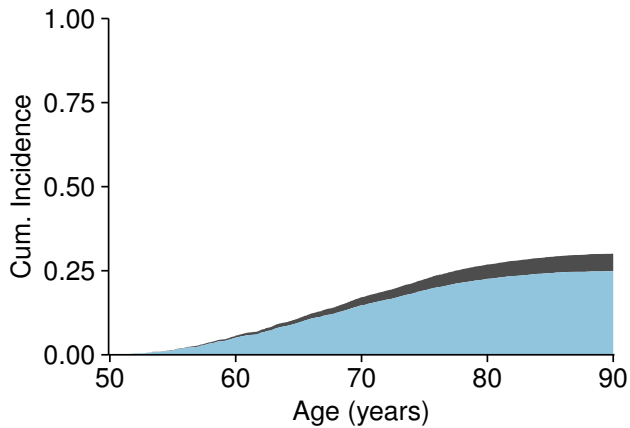**B**   Prostate Cancer Death

Genetic risk

■ PRS 0–50%, no FH
■ PRS 50–100% or FH