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ORIGINAL REPORT

Relationship Between Male Pattern Baldness and the Risk of Aggressive Prostate Cancer: An Analysis of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

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ABSTRACT

Purpose

Male pattern baldness and prostate cancer appear to share common pathophysiologic mechanisms. However, results from previous studies that assess their relationship have been inconsistent. Therefore, we investigated the association of male pattern baldness at age 45 years with risks of overall and subtypes of prostate cancer in a large, prospective cohort—the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.

Methods

We included 39,070 men from the usual care and screening arms of the trial cohort who had no cancer diagnosis (excluding nonmelanoma skin cancer) at the start of follow-up and recalled their hair-loss patterns at age 45 years. Hazard ratios (HRs) and 95% CIs were estimated by using Cox proportional hazards regression models with age as the time metric.

Results

During follow-up (median, 2.78 years), 1,138 incident prostate cancer cases were diagnosed, 571 of which were aggressive (biopsy Gleason score ≥ 7, and/or clinical stage III or greater, and/or fatal). Compared with no baldness, frontal plus moderate vertex baldness at age 45 years was not significantly associated with overall (HR, 1.19; 95% CI, 0.98 to 1.45) or nonaggressive (HR, 0.97; 95% CI, 0.72 to 1.30) prostate cancer risk but was significantly associated with increased risk of aggressive prostate cancer (HR, 1.39; 95% CI, 1.07 to 1.80). Adjustment for covariates did not substantially alter these estimates. Other classes of baldness were not significantly associated with overall or subtypes of prostate cancer.

Conclusion

Our analysis indicates that frontal plus moderate vertex baldness at age 45 years is associated with an increased risk of aggressive prostate cancer and supports the possibility of common pathophysiologic mechanisms.

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INTRODUCTION

In US men, prostate cancer is the most frequently diagnosed noncutaneous cancer and the second leading cause of cancer death.[1] Few risk factors have been established for prostate cancer except for advancing age, black race, family history of this malignancy,[2-4] and certain genetic polymorphisms,[5,6] which collectively explain only a fraction of the disease occurrence. Therefore, additional research to improve our understanding of the etiology of prostate cancer is needed. Male pattern baldness (or androgenic alopecia) seems to share pathologic mechanisms with prostate cancer in terms of advancing age, hereditability, and endogenous hormones.[2,7] The fact that the age of observable hair loss coincides with the age of microscopic evidence for prostate cancer in autopsy studies,[8,9] and that male pattern baldness represents cumulative exposures, as opposed to a single serum measurement, may help elucidate prostate cancer etiology.

Results from previous epidemiologic studies on the association between male pattern baldness and prostate cancer risk are inconclusive.[10-22] Most studies were of cross-sectional or case-control design with small sample sizes and limited statistical power. Two cohort studies, as well as a meta-analysis of seven case-control studies, have suggested a positive association between male pattern baldness and prostate cancer risk,[19,21,23] but subtype-specific

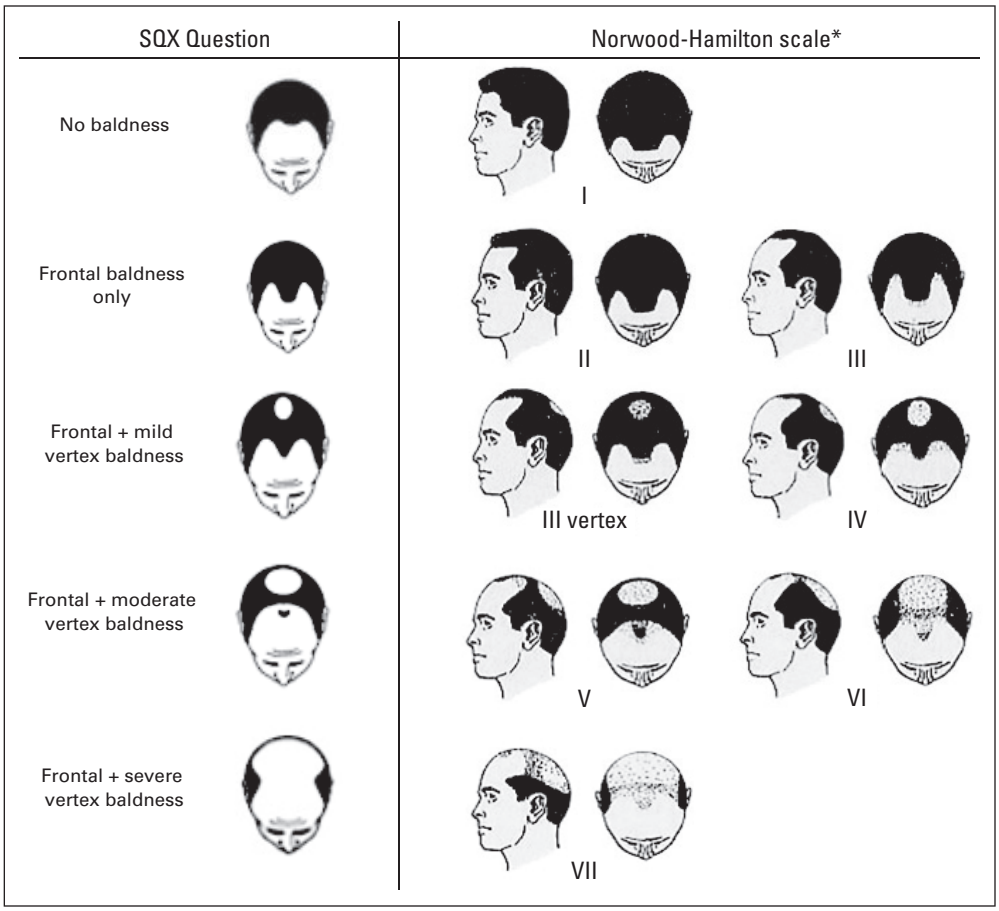

Fig 1. Male pattern baldness at age 45 years as elicited in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial Supplemental Questionnaire (SQX). (*) Scale image reproduced.[26]

analyses by prostate cancer aggressiveness were not presented. To overcome the noted shortfalls, we conducted an analysis of male pattern baldness at age 45 years in relation to risks of overall and subtypes of prostate cancer in the prospective Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.

METHODS

The analytic cohort was drawn from the PLCO Cancer Screening Trial, the design of which has been described in detail previously.[24,25] In brief, the trial was a multicenter, randomized, two-arm trial evaluating the effect of screening on disease-specific mortality end points. This study was approved by the institutional review boards of the National Cancer Institute and the 10 US screening centers.

Screening centers enrolled 76,683 men from 1993 to 2001. Eligible men were age 55 to 74 years at enrollment; had no history of prostate, lung, or colorectal cancer; had not undergone surgical removal of the entire prostate, a lung, or the entire colon; were not undergoing treatment for cancer (except nonmelanoma skin cancer [NMSC]); had not taken finasteride (Proscar) in the past 6 months; had no more than one prostate-specific antigen (PSA) test in the past 3 years from April 15, 1995 (date of trial protocol change). Eligible men were randomly assigned into the screening arm (ie, annual PSA test for the first 6 years, and annual digital rectal examination for the first 4 years), or the usual care arm. Men with suspected prostate cancer from an abnormal PSA test ($>$ 4.0 ng/mL) and/or digital rectal examination result were referred for diagnostic work-up. Around the time of random assignment, each man was mailed a sex-specific baseline questionnaire–men (BQM). From 2006 to 2008, men who remained under active follow-up (Appendix Fig A1, online only) were mailed a supplemental questionnaire (SQX) to expand risk factor ascertainment.

Exposure Ascertainment

In the SQX, participants were asked to recall their hair-loss patterns at age 45 years from a modified Norwood-Hamilton scale (Fig 1): (1) no baldness, (2) frontal baldness only, (3) frontal plus mild vertex baldness, (4) frontal plus moderate vertex baldness, and (5) frontal plus severe vertex baldness.[26]

Outcome Ascertainment

Diagnosed cancers and deaths were ascertained by active follow-up using annual mailed study update questionnaires, supplemented by linkage to the National Death Index. Cancer diagnoses were confirmed by medical record abstraction. Underlying causes of death were determined via a death review process that used information from death certificates as well as medical documents.[27] In this analysis, incident prostate cancer was defined as having a first cancer diagnosis (excluding NMSC) of prostate cancer, or a second cancer diagnosis of prostate cancer within 30 days of the first cancer diagnosis because we considered that such close proximity of two primary cancer diagnoses indicated synchronous emergence.

Analytic Cohort

The analytic cohort comprised men from both trial arms who had no cancer diagnosis (excluding NMSC) at start of follow-up (ie, the time of the SQX) and who responded to the balding question. This resulted in a total of 39,070 men in the SQX cohort. Appendix Figure A1 describes exclusions that were used to form the analytic cohort.

Statistical Analyses

Pearson χ^2 tests were used for categorical characteristics by case status and male pattern baldness. Cox proportional hazards regression models, with

age in months as the time metric, were used to estimate hazards ratios (HRs) and 95% CIs of associations between male pattern baldness and prostate cancer risk. Follow-up started from age at SQX and continued until age at event (ie, incident prostate cancer defined above) or age at time of right-censoring (ie, study withdrawal, diagnosis with non–prostate cancer [excluding NMSC], death as a result of other causes, last date of follow-up), whichever occurred first.

The percentage of missing values was lower than 10% at BQM and SQX for all variables considered, except for family income (15%) and family history of prostate cancer (12%). For these missing values, we conducted multiple imputation using BQM and SQX data by a sequence of regression models[28] via IVEware[29] in SAS (SAS Institute, Cary, NC). Self-reported race was highly consistent across the two questionnaires. We thus used race reported at BQM if race at SQX was missing and imputed race if it was missing on both questionnaires (4%). Five imputed data sets were created and analyzed individually, and then HR estimates were combined by using PROC MIANALYZE in SAS. Proportional hazards assumptions were tested by using interaction terms and through visual inspection of log(-log) survival plots.

To explore the impact of possible confounders on the association between male pattern baldness and prostate cancer risk, we calculated HRs (95% CIs) by using unadjusted models and multivariable models adjusted for screening arm, screening center, race, education, marital status, cigarette smoking, body mass index (kg/m^2) at age 50 years, regular aspirin use, history of diabetes, and history of myocardial infarction. Covariates chosen for the multivariable models had P values less than .15 in relation to both prostate cancer and male pattern baldness in univariable models (ie, χ^2 tests) or were deemed a priori as potential confounders (screening arm, marital status, and diabetes). In addition, we adjusted for covariates that are potentially pathophysiologically related to prostate cancer (family history of prostate cancer in first-degree relative[s], and history of enlarged prostate).

We conducted subtype-specific analyses by prostate cancer aggressiveness, with aggressive defined as biopsy Gleason score ≥ 7, and/or clinical stage III or greater, and/or fatal prostate cancer (ie, as the underlying cause of death). For these analyses, men who experienced a prostate cancer subtype that was not of interest were censored at diagnosis. For example for aggressive prostate cancer, we censored men at the age at diagnosis of a nonaggressive tumor. To evaluate the robustness of associations, we also performed subtype-specific analyses by different definitions of aggressive prostate cancer: (1) biopsy Gleason score ≥ 8, and/or clinical stage III or greater, and/or fatal prostate cancer; (2) comprehensive Gleason score (from prostatectomy or biopsy) ≥ 7, and/or comprehensive stage (from pathologic or clinical TNMs) III or greater, and/or fatal prostate cancer; (3) comprehensive Gleason score ≥ 8, and/or comprehensive stage III or greater, and/or fatal prostate cancer; (4) modified D'Amico criteria[30,31] as low risk (cT1 to cT2a, prediagnostic PSA within 6 months ≤ 10 ng/mL, and biopsy Gleason score ≤ 6); intermediate risk (cT2b, and/or prediagnostic PSA within 6 months > 10 ng/mL and ≤ 20 ng/mL, and/or biopsy Gleason score $= 7$); and high risk ($\geq$ cT2c, and/or prediagnostic PSA within 6 months > 20 ng/mL, and/or biopsy Gleason score ≥ 8, and/or fatal prostate cancer). Other sensitivity analyses included combining classes of male pattern baldness (no/frontal only/frontal plus any vertex baldness; any/no baldness), adjusting for recall period from age 45 years to age at SQX, and restriction to men enrolled after trial protocol change. SAS v.9.3 was used for analyses. Two-sided $P < .05$ was considered statistically significant.

RESULTS

Of the 39,070 men in our analytic cohort, male pattern baldness at age 45 years was reported by 53.4%, of which 46.4% reported frontal baldness only, 23.5% frontal plus mild vertex baldness, 18.1% frontal plus moderate vertex baldness, and 12.0% frontal plus severe vertex baldness. During follow-up (median, 2.78 years), 1,138 incident prostate cancers were diagnosed, 571 of which were aggressive (biopsy Gleason score ≥ 7, and/or clinical stage III or greater, and/or fatal). The mean age at prostate cancer diagnosis was 72.2 years (range, 61.4 to 86.5 years).

Table 1 provides the characteristics of the analytic cohort by case status. The analytic cohort was predominantly white (89.3%). Compared with men without prostate cancer, men with aggressive prostate cancer were more likely to be in the usual care arm, married/cohabiting, have a history of enlarged prostate, and were less likely to ever smoke cigarettes; men with nonaggressive prostate cancer were more likely to be married/cohabiting, have a family history of prostate cancer, have a history of enlarged prostate, and were less likely to ever smoke cigarettes, and to have a history of diabetes or myocardial infarction.

Table 2 provides data showing that male pattern baldness at age 45 years was not significantly associated with overall prostate cancer risk, although frontal plus moderate vertex baldness showed a nonsignificant increased risk of approximately 19% compared with no baldness in the unadjusted model (HR, 1.19; 95% CI, 0.98 to 1.45). However, frontal plus moderate vertex baldness was significantly associated with an increased risk of aggressive prostate cancer compared with no baldness in the unadjusted model (HR, 1.39; 95% CI, 1.07 to 1.80). Conversely, classes of male pattern baldness were not significantly associated with nonaggressive prostate cancer. Further adjustment did not substantially alter the HR estimates.

Sensitivity analyses by different definitions of aggressive prostate cancer showed stronger associations between frontal plus moderate vertex baldness and aggressive prostate cancer (Appendix Table A1, online only). Combined classes of male pattern baldness were not significantly associated with prostate cancer (Table 1). Additional adjustment for recall period, or covariates—which are potentially pathophysiologically related to prostate cancer—did not materially affect results (results not shown). Restriction to men enrolled after the date of trial protocol change (Appendix Table A2, online only) did not appreciably alter results.

DISCUSSION

In this large prospective study, frontal plus moderate vertex baldness at age 45 years was significantly associated with an increased risk of aggressive prostate cancer compared with no baldness. Other classes of baldness were not associated with aggressive prostate cancer, and no class of baldness was significantly associated with overall or nonaggressive prostate cancer.

Although the association between male pattern baldness and prostate cancer has been inconsistent, two recent cohort studies[19,21] and a meta-analysis[23] suggested a positive relationship. The National Health and Nutrition Examination Survey I (NHANES I) Epidemiologic Follow-up Study (NHEFS), which accrued 214 incident prostate cancer cases in 4,421 men during 20 years of follow-up, reported an HR of 1.50 (95% CI, 1.12 to 2.00) for prostate cancer in relation to any degree of baldness, as examined by dermatology residents at baseline.[21] However, more than half the men were older than age 55 years at baseline. The other cohort study—the Melbourne Collaborative Cohort Study (MCCS)—comprised 9,448 men, 476 of whom were diagnosed with prostate cancer during 11 years of follow-up. This study predicted a 1.81 times (95% CI, 1.13 to 2.90 times) higher risk of prostate cancer by age 55 years among men with vertex baldness (Norwood-Hamilton scale III vertex to VII) at age 40 years than those without baldness, although the HR dropped to 1.00 by age 60 to 70 years.[19] However, male pattern baldness was recalled after the diagnosis of prostate cancer, and men with aggressive prostate cancer were more likely to have missing exposure because of loss to

Table 1. Characteristics of Patients in the Analytic Cohort by Case Status

Characteristic	Non–Prostate Cancer		Incident Prostate Cancer								
			Total (N = 1,138)			Aggressive* (n = 571)			Nonaggressive* (n = 552)		
	No.	%	No.	%	P†	No.	%	P†	No.	%	P†
Randomly assigned group					.032			.013			.801
Usual care	18,143	47.8	581	51.1		303	53.1		267	48.4	
Intervention	19,789	52.2	557	48.9		268	46.9		285	51.6	
Age at SQX (years)					< .001			.170			< .001
< 65	5,378	14.2	161	14.1		70	12.3		88	15.9	
65-69	10,985	29.0	388	34.1		166	29.1		216	39.1	
70-74	9,896	26.1	319	28.0		170	29.8		147	26.6	
≥ 75	11,673	30.8	270	23.7		165	28.9		101	18.3	
Median	71		70			71			69		
IQR	66-76		66-74			67-75			66-73		
Education					.021			.061			.407
Less than high school	2,211	5.8	45	4.0		20	3.5		23	4.2	
High school graduate	11,237	29.6	348	30.6		177	31.0		167	30.3	
Some college	7,560	19.9	226	19.9		113	19.8		109	19.7	
College graduate	7,661	20.2	212	18.6		104	18.2		107	19.4	
Postgraduate	9,173	24.2	305	26.8		156	27.3		146	26.4	
Marital status					< .001			.015			< .001
Married or cohabiting	30,888	81.4	978	85.9		488	85.5		478	86.6	
Single‡	6,721	17.7	151	13.3		79	13.8		69	12.5	
Race					.137			.305			.376
White	33,871	89.3	1,023	89.9		511	89.5		498	90.2	
Black	841	2.2	34	3.0		18	3.2		16	2.9	
Other§	1,684	4.4	43	3.8		23	4.0		20	3.6	
First-degree relative(s) had prostate cancer					< .001			.222			< .001
No	30,129	79.4	853	75.0		438	76.7		402	72.8	
Yes	3,297	8.7	138	12.1		57	10.0		80	14.5	
Diabetes					.037			.279			< .001
No	27,581	72.7	867	76.2		410	71.8		444	80.4	
Yes	6,207	16.4	163	14.3		104	18.2		59	10.7	
Myocardial infarction					.008			.257			.005
No	28,137	74.2	875	76.9		427	74.8		438	79.3	
Yes	5,343	14.1	129	11.3		70	12.3		56	10.1	
Enlarged prostate					< .001			.008			< .001
No	20,710	54.6	510	44.8		280	49.0		220	39.9	
Yes	16,889	44.5	619	54.4		286	50.1		328	59.4	
BMI at age 50 years (kg/m^2)					.036			.126			.265
< 25.0	12,341	32.5	380	33.4		201	35.2		178	32.2	
25.0-29.9	17,026	44.9	537	47.2		262	45.9		263	47.6	
≥ 30	5,264	13.9	129	11.3		64	11.2		65	11.8	
Cigarette smoking					.001			.022			.007
Never	12,999	34.3	442	38.8		220	38.5		220	39.9	
Ever	23,771	62.7	659	57.9		329	57.6		317	57.4	
Aspirin use frequency					.097			.242			.442
None or < 1 time per month	11,581	30.5	328	28.8		164	28.7		159	28.8	
≤ 2 times per week	3,668	9.7	113	9.9		56	9.8		56	10.1	
3-6 times per week	3,906	10.3	102	9.0		49	8.6		51	9.2	
≥ 7 times per week	17,903	47.2	581	51.1		293	51.3		281	50.9	
Male pattern baldness at age 45 years					.368			.119			.981
No baldness	17,678	46.6	522	45.9		257	45.0		260	47.1	
Any baldness	20,254	53.4	616	54.1	.750‖	314	55.0	.500‖	292	52.9	.904‖
Frontal baldness only	9,411	24.8	279	24.5		138	24.2		139	25.2	
Frontal plus any vertex baldness	9,411	24.8	279	24.5	.625¶	138	24.2	.448¶	139	25.2	.816¶
Frontal plus mild vertex baldness	4,760	12.5	142	12.5		68	11.9		69	12.5	

(continued on following page)

Table 1. Characteristics of Patients in the Analytic Cohort by Case Status (continued)

Characteristic	Non–Prostate Cancer		Incident Prostate Cancer: Total (N = 1,138)			Incident Prostate Cancer: Aggressive* (n = 571)			Incident Prostate Cancer: Nonaggressive* (n = 552)		
	No.	%	No.	%	P†	No.	%	P†	No.	%	P†
Frontal plus moderate vertex baldness	3,643	9.6	129	11.3		74	13.0		52	9.4	
Frontal plus severe vertex baldness	2,440	6.4	66	5.8		34	6.0		32	5.8	

NOTE. Column percent may not add up to 100% because of missing data.
Abbreviations: BMI, body mass index; IQR, interquartile range; SQX, supplemental questionnaire.
*Aggressive prostate cancer was defined as biopsy Gleason score ≥ 7, and/or clinical stage III or greater, and/or prostate cancer as underlying cause of death. Nonaggressive prostate cancer was defined as otherwise. Fifteen prostate cancers lacked enough information to determine prostate cancer subtypes.
†*P* values were calculated by Pearson χ^2 tests by using nonmissing values with comparison to controls without cancer.
‡Single includes widowed, divorced, separated, and never married.
§Other race includes Asian, Native Hawaiian or other Pacific Islander, American Indian, or Alaskan Native.
‖*P* value was calculated for any baldness and no baldness by Pearson χ^2 tests compared with controls without cancer.
¶*P* value was calculated for frontal baldness only, frontal plus any vertex baldness, and no baldness by Pearson χ^2 tests compared with controls without cancer.

follow-up. Finally, a meta-analysis of seven case-control studies reported that men with any vertex baldness had an odds ratio (OR) of 1.25 (95% CI, 1.09 to 1.44) for prostate cancer compared with those without baldness, although no significant association was found for frontal recession only.[23]

We found no significant association of any classes of male pattern baldness at age 45 years with overall prostate cancer risk. This result is consistent with the MCCS null result for men age 60 to 70 years,[19] a fair comparison to our study, given that the youngest age at the start of follow-up in our analytic cohort was 60 years. It is possible that, in relation to overall prostate cancer risk diagnosed in a population with high use of PSA screening, male pattern baldness is associated only with early-onset disease.

We found a significant and robust association between frontal plus moderate vertex baldness and increased risk of aggressive prostate cancer. This result is supported by similar associations observed in the NHEFS in which two thirds of follow-up occurred in the pre-PSA era, a period when a greater proportion of prostate cancer cases were identified symptomatically. In addition, akin to the MCCS, positive results in the NHEFS may also be partly attributable to an average younger cohort (median age, 55.1 years),[21] if our prior hypothesis of an association between male pattern baldness and early-onset disease is true. Our result of the importance of frontal plus moderate vertex baldness in relation to aggressive prostate cancer may also be supported by a matched case-control study in Australian men, which reported a positive association (OR, 2.04; 95% CI, 1.35 to 3.08) of high-grade (Gleason scores 8 to 10) prostate cancer with vertex balding (Norwood-Hamilton stage III vertex and stage V) assessed by interviewers.[12]

We found no significant association between the highest class of male pattern baldness (frontal plus severe baldness) and prostate cancer risk. This observation may be explained by the failure to include younger men with prostate cancer or fatal/severe cardiovascular disease[32,33] before start of follow-up (SQX), if this highest class of baldness is associated with such; measurement errors of recalled hair-loss via a modified Norwood-Hamilton scale; or different biologic mechanisms of balding patterns or extent. In addition, we did not find any significant association between the highest composite class of male pattern baldness (frontal with any vertex baldness) and prostate cancer risk; our observed association with frontal plus moderate vertex

Table 2. Associations Between Male Pattern Baldness at Age 45 Years and Prostate Cancer Risk in the Analytic Cohort

Male Pattern Baldness at Age 45 Years	Total Incident Prostate Cancer (N = 1,138)				Aggressive Prostate Cancer* (n = 571)				Nonaggressive Prostate Cancer* (n = 552)			
	Unadjusted†		Multivariable‡		Unadjusted†		Multivariable‡		Unadjusted†		Multivariable‡	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
No baldness	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Any baldness	1.03	0.92 to 1.16	1.02	0.91 to 1.15	1.07	0.90 to 1.26	1.06	0.90 to 1.25	0.98	0.83 to 1.16	0.97	0.82 to 1.15
Frontal baldness only	1.00	0.87 to 1.16	1.00	0.86 to 1.16	1.00	0.82 to 1.23	1.00	0.81 to 1.23	1.01	0.82 to 1.24	1.00	0.82 to 1.23
Frontal plus any vertex baldness	1.05	0.92 to 1.21	1.04	0.91 to 1.20	1.12	0.92 to 1.36	1.11	0.92 to 1.35	0.96	0.78 to 1.17	0.95	0.77 to 1.16
Frontal plus mild vertex baldness	1.01	0.84 to 1.21	1.00	0.83 to 1.20	0.99	0.76 to 1.29	0.98	0.75 to 1.28	0.97	0.75 to 1.27	0.96	0.74 to 1.25
Frontal plus moderate vertex baldness	1.19	0.98 to 1.45	1.19	0.98 to 1.45	1.39	1.07 to 1.80	1.39	1.07 to 1.80	0.97	0.72 to 1.30	0.96	0.71 to 1.30
Frontal plus severe vertex baldness	0.93	0.72 to 1.20	0.92	0.71 to 1.19	0.97	0.68 to 1.39	0.97	0.68 to 1.39	0.90	0.63 to 1.30	0.89	0.61 to 1.28

NOTE. Missing values of covariates (excluding male pattern baldness at age 45 years) were imputed in sequential regression multiple imputation models via IVEware in SAS v.9.3.
Abbreviations: HR, hazard ratio; Ref., reference.
*Aggressive prostate cancer was defined as biopsy Gleason score ≥ 7, and/or clinical stage III or greater, and/or prostate cancer as underlying cause of death. Nonaggressive prostate cancer was defined as otherwise. Fifteen prostate cancers lacked enough information to determine prostate cancer subtypes.
†Unadjusted model: age (month) was used as the underlying time metric.
‡Multivariable model: adjusted for screening arm (usual care, screening), screening center (10 centers, not listed here), race (white, black, other), education (less than high school, high school graduate, some college, college graduate, postgraduate), married or cohabiting (yes, no), diabetes (yes, no), body mass index at age 50 years (< 18.5, 18.5-24.9, 25.0-29.9, ≥ 30 kg/m^2), cigarette smoking (ever, never), aspirin use frequency (none or < 1 time per month, ≤ 2 times per week, 3-6 times per week, ≥ 7 times per week), and myocardial infarction (yes, no).

baldness and aggressive prostate cancer was masked by using this combined exposure.

Results from basic science and observational studies have suggested an association between male pattern baldness and prostate cancer with respect to aging, hereditability, and endogenous hormones. Advancing age is accompanied by increasing incidence and extent of baldness,[34] as well as by increasing prostate cancer mortality.[35] With regard to hereditability, it has been estimated that 42% of prostate cancer[36] and 81% of male pattern baldness[37] are attributed to heritable factors in twin studies. Moreover, two loci (Xq12 and 3q26) identified in genome-wide association studies of European men have separately been found to be associated with prostate cancer[38] and male pattern baldness.[39-42] Evidence for the importance of sex steroid hormones comes from the fact that hair follicles and the prostate gland are both androgen responsive. Men born with a congenital deficiency of 5-alpha reductase type II or who were prepubertally castrated do not develop prostate cancer and show complete retention of scalp hair.[43] Baldness has also been associated with higher levels of dihydrotestosterone[44] and increased expression of androgen receptor.[45-47] Epidemiologic evidence for associations between circulating androgens and prostate cancer is inconclusive.[48-50] Limitations of these studies include between-assay variations, lack of comparability of androgen levels, and use of a single blood measurement typically at middle age or later. Meanwhile, genetic polymorphisms in *SRD5A2*,[51] *CYP17*,[52] and *HSD3B*[53] androgen metabolism genes as well as genomic regulatory elements binding to androgen receptor[54,55] have been associated with prostate cancer, thus supporting the importance of sex steroid hormones.

Besides androgenic action, circulating insulin-like growth factors (IGFs) and hyperinsulinemia may also play roles in prostate carcinogenesis and baldness either directly or via interactions with androgens. A meta-analysis of 42 epidemiologic studies (14 cohort and 28 case-controls studies) reported that circulating IGF-I was associated with increased risk of prostate cancer.[56] In addition, two case-control studies suggested that vertex balding was positively associated with increased circulating IGF-1 and inversely associated with plasma IGF binding protein-3.[57,58] Moreover, hyperinsulinemia has been reported to be associated with accelerated growth of prostate cancer xenografts,[59-61] as well as increased prostate cancer risk in two case-control studies.[62,63] Insulin resistance can also lead to vasoconstriction and nutritional deficits in scalp follicles preceding hair loss,[64,65] and minoxidil (an antihypertensive vasodilator) has been used to treat hair loss.

Several limitations of this study warrant discussion. First, the validity and reliability of our modified Norwood-Hamilton scale has not been assessed. However, previous validation studies for similar adapted scales showed that the validity (kappa = 0.47 to 0.60) of self-reported current hair patterns[66,67] and reliability (kappa = 0.71 ± 0.07) of recalling hair patterns at age 45 years were moderate to good.[66] Second, exposure was retrospectively recalled, which could have an impact on the accuracy of reporting. However, differential misclassification of exposure is not expected, given that exposure was recalled before prostate cancer diagnosis. Third, only a small number of black men were included in our cohort. In the NHEFS, black men with any degree of baldness had increased risk of prostate cancer (relative risk [RR], 2.10; 95% CI, 1.04 to 4.25).[21] A case-control study in African American men showed that baldness at age 30 years recalled on a modified Norwood-Hamilton scale was significantly associated with prostate cancer risk (OR, 1.69; 95% CI, 1.05 to 2.74).[20] Moreover, this case-control study demonstrated that frontal baldness was more strongly associated with high-stage (OR, 2.61; 95% CI, 1.10 to 6.18) and high-grade prostate cancer (OR, 2.20; 95% CI, 1.05 to 4.61).[20] However, the paradox that black men are less likely to have male pattern baldness than their white counterparts[68] (Appendix Table A3, online only) but have higher risk for prostate cancer requires further elucidation. Finally, we had only one single age point of male pattern baldness in this study, and a broader age range of male pattern baldness assessment may be more informative.

In summary, our analysis of the prospective PLCO Cancer Screening Trial has shown a positive association between frontal plus moderate vertex baldness at age 45 years and aggressive prostate cancer risk. Although the effect is moderate, it supports the possibility of overlapping pathogeneses between male pattern baldness and prostate cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Appendix

Table A1. Associations Between Male Pattern Baldness at Age 45 Years and Prostate Cancer Risk in the Analytic Cohort by Four Different Definitions of Prostate Cancer Aggressiveness

	Unadjusted*		Multivariable†		Unadjusted*		Multivariable†		Unadjusted*		Multivariable†	
Male Pattern Baldness at Age 45 Years	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
	Definition 1‡											
	Aggressive (n = 169)				Nonaggressive (n = 953)							
No baldness	Ref.		Ref.		Ref.		Ref.					
Any baldness	1.27	0.93 to 1.72	1.26	0.93 to 1.71	0.98	0.87 to 1.12	0.98	0.86 to 1.11				
Frontal baldness only	1.21	0.83 to 1.77	1.21	0.83 to 1.76	0.97	0.83 to 1.14	0.96	0.82 to 1.13				
Any frontal plus vertex baldness	1.31	0.92 to 1.87	1.30	0.91 to 1.86	1.00	0.86 to 1.16	0.99	0.85 to 1.15				
Frontal plus mild vertex baldness	1.15	0.70 to 1.87	1.14	0.70 to 1.87	0.96	0.78 to 1.17	0.94	0.77 to 1.16				
Frontal plus moderate vertex baldness	2.03	1.32 to 3.13	2.02	1.31 to 3.12	1.05	0.84 to 1.30	1.04	0.84 to 1.30				
Frontal plus severe vertex baldness	0.53	0.22 to 1.32	0.53	0.21 to 1.30	1.00	0.76 to 1.30	0.99	0.76 to 1.30				
	Definition 2§											
	Aggressive (n = 628)				Nonaggressive (n = 502)							
No baldness	Ref.		Ref.		Ref.		Ref.					
Any baldness	1.09	0.93 to 1.28	1.08	0.93 to 1.27	0.96	0.81 to 1.15	0.95	0.80 to 1.14				
Frontal baldness only	1.07	0.88 to 1.30	1.06	0.87 to 1.29	0.95	0.76 to 1.18	0.94	0.76 to 1.17				
Any frontal plus vertex baldness	1.11	0.92 to 1.34	1.11	0.92 to 1.33	0.97	0.79 to 1.20	0.96	0.78 to 1.19				
Frontal plus mild vertex baldness	1.00	0.77 to 1.29	0.99	0.77 to 1.28	0.99	0.75 to 1.30	0.97	0.74 to 1.28				
Frontal plus moderate vertex baldness	1.42	1.11 to 1.81	1.42	1.11 to 1.81	0.93	0.68 to 1.28	0.93	0.68 to 1.27				
Frontal plus severe vertex baldness	0.87	0.60 to 1.24	0.87	0.60 to 1.24	1.01	0.70 to 1.46	0.99	0.69 to 1.43				
	Definition 3‖											
	Aggressive (n = 219)				Nonaggressive (n = 911)							
No baldness	Ref.		Ref.		Ref.		Ref.					
Any baldness	1.28	0.98 to 1.67	1.28	0.98 to 1.68	0.98	0.86 to 1.12	0.97	0.85 to 1.11				
Frontal baldness only	1.22	0.88 to 1.70	1.22	0.88 to 1.71	0.97	0.82 to 1.14	0.96	0.82 to 1.13				
Any frontal plus vertex baldness	1.33	0.97 to 1.81	1.33	0.97 to 1.82	0.99	0.85 to 1.16	0.98	0.84 to 1.14				
Frontal plus mild vertex baldness	1.17	0.77 to 1.80	1.18	0.77 to 1.80	0.96	0.78 to 1.18	0.94	0.76 to 1.16				
Frontal plus moderate vertex baldness	1.96	1.33 to 2.89	1.97	1.34 to 2.91	1.04	0.83 to 1.30	1.03	0.82 to 1.29				
Frontal plus severe vertex baldness	0.66	0.32 to 1.36	0.66	0.32 to 1.36	0.99	0.75 to 1.30	0.98	0.75 to 1.29				
	Definition 4¶											
	High Risk (n = 187)				Intermediate Risk (n = 400)				Low Risk (n = 415)			
No baldness	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Any baldness	1.17	0.87 to 1.56	1.16	0.87 to 1.55	1.06	0.87 to 1.30	1.07	0.88 to 1.30	0.98	0.81 to 1.18	0.97	0.80 to 1.18
Frontal baldness only	1.07	0.75 to 1.54	1.07	0.74 to 1.53	1.04	0.81 to 1.33	1.04	0.81 to 1.33	1.02	0.81 to 1.30	1.02	0.80 to 1.29
Any frontal plus vertex baldness	1.25	0.90 to 1.75	1.24	0.89 to 1.73	1.09	0.86 to 1.37	1.09	0.87 to 1.38	0.94	0.74 to 1.18	0.93	0.74 to 1.17
Frontal plus mild vertex baldness	1.08	0.68 to 1.72	1.07	0.67 to 1.71	1.03	0.75 to 1.41	1.03	0.75 to 1.41	0.93	0.68 to 1.27	0.92	0.67 to 1.25
Frontal plus moderate vertex baldness	1.93	1.28 to 2.91	1.92	1.27 to 2.90	1.12	0.80 to 1.57	1.13	0.81 to 1.59	0.96	0.68 to 1.36	0.97	0.68 to 1.36
Frontal plus severe vertex baldness	0.55	0.24 to 1.26	0.54	0.24 to 1.25	1.14	0.76 to 1.69	1.16	0.78 to 1.73	0.90	0.59 to 1.37	0.89	0.58 to 1.36

NOTE. Missing values of covariates (excluding male pattern baldness at age 45 years) were imputed in sequential regression multiple imputation models via IVEware in SAS v.9.3. Unadjusted model: age (month) was used as the underlying time metric. Multivariable model: adjusted for screening arm (usual care, screening), screening center (10 centers, not listed here), race (white, black, other), education (less than high school, high school graduate, some college, college graduate, postgraduate), married or cohabiting (yes, no), diabetes (yes, no), body mass index at age 50 years (< 18.5, 18.5-24.9, 25.0-29.9, ≥ 30 kg/m^2), cigarette smoking (ever, never), aspirin use frequency (none or < 1 time per month, ≤ 2 times per week, 3-6 times per week, ≥ 7 times per week), and myocardial infarction (yes, no).

Abbreviations: HR, hazard ratio; Ref., reference.

*Definition 1: aggressive prostate cancer was defined as biopsy Gleason score ≥ 8, and/or clinical stage III or greater, and/or fatal prostate cancer. There were 16 prostate cancers that lacked enough information to determine prostate cancer subtypes.

†Definition 2: aggressive prostate cancer was defined as comprehensive Gleason score ≥ 7, and/or comprehensive stage III or greater, and/or fatal prostate cancer. There were eight prostate cancers that lacked enough information to determine prostate cancer subtypes.

‡Definition 3: aggressive prostate cancer was defined as comprehensive Gleason score ≥ 8, and/or comprehensive stage III or greater, and/or fatal prostate cancer. There were eight prostate cancers that lacked enough information to determine prostate cancer subtypes.

§Definition 4: modified D'Amico criteria: low risk (cT1 to cT2a, prediagnostic prostate-specific antigen [PSA] within 6 months ≤ 10 ng/mL, and biopsy Gleason score ≤ 6); intermediate risk (cT2b, and/or prediagnostic PSA within 6 months > 10 ng/mL and ≤ 20 ng/mL, and/or biopsy Gleason score of 7); and high risk ($\geq$ cT2c, and/or prediagnostic PSA within 6 months > 20 ng/mL, and/or biopsy Gleason score ≥ 8, and/or fatal prostate cancer). There were 136 prostate cancers that lacked enough information to determine prostate cancer subtypes.

Table A2. Sensitivity Analysis: Associations Between Male Pattern Baldness at Age 45 Years and Prostate Cancer Risk in the Analytic Cohort Restricted to the Subcohort of Individuals Enrolled After the Date of Trial Protocol Change (N = 33,367)

Male Pattern Baldness at Age 45 Years	Total Incident Prostate Cancer (N = 1,053)				Aggressive Prostate Cancer* (n = 517)				Nonaggressive Prostate Cancer* (n = 521)			
	Unadjusted†		Multivariable‡		Unadjusted†		Multivariable‡		Unadjusted†		Multivariable‡	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
No baldness	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Any baldness	1.06	0.93 to 1.19	1.04	0.92 to 1.18	1.11	0.93 to 1.32	1.10	0.92 to 1.31	0.99	0.83 to 1.18	0.97	0.82 to 1.16
Frontal baldness only	1.04	0.90 to 1.21	1.03	0.89 to 1.20	1.05	0.85 to 1.31	1.04	0.84 to 1.30	1.04	0.84 to 1.28	1.02	0.83 to 1.26
Any frontal plus vertex baldness	1.07	0.93 to 1.23	1.05	0.91 to 1.22	1.16	0.95 to 1.42	1.15	0.94 to 1.41	0.95	0.77 to 1.17	0.93	0.76 to 1.15
Frontal plus mild vertex baldness	1.03	0.85 to 1.25	1.01	0.84 to 1.23	1.06	0.81 to 1.40	1.05	0.79 to 1.38	0.94	0.71 to 1.24	0.93	0.70 to 1.22
Frontal plus moderate vertex baldness	1.19	0.98 to 1.46	1.19	0.97 to 1.45	1.40	1.06 to 1.84	1.39	1.06 to 1.83	0.97	0.71 to 1.32	0.96	0.70 to 1.30
Frontal plus severe vertex baldness	0.95	0.73 to 1.23	0.93	0.72 to 1.22	0.99	0.68 to 1.44	0.99	0.68 to 1.44	0.93	0.64 to 1.35	0.90	0.62 to 1.31

NOTE. Missing values of covariates (excluding male pattern baldness at age 45 years) were imputed in sequential regression multiple imputation models via IVEware in SAS v.9.3.

Abbreviations: HR, hazard ratio; Ref., reference.

*Aggressive prostate cancer was defined as biopsy Gleason score ≥ 7, and/or clinical stage III or greater, and/or prostate cancer as underlying cause of death. Nonaggressive prostate cancer was defined as otherwise. Fourteen prostate cancers lacked enough information to determine prostate cancer subtypes.

†Unadjusted model: age (month) was used as the underlying time metric.

‡Multivariable model: adjusted for screening arm (usual care, screening), screening center (10 centers, not listed here), race (white, black, other), education (less than high school, high school graduate, some college, college graduate, postgraduate), married or cohabiting (yes, no), diabetes (yes, no), body mass index at age 50 years (< 18.5, 18.5-24.9, 25.0-29.9, ≥ 30 kg/m^2), cigarette smoking (ever, never), aspirin use frequency (none or < 1 time per month, ≤ 2 times per week, 3-6 times per week, ≥ 7 times per week), and myocardial infarction (yes, no).

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Table A3. Characteristics of Participants in the Analytic Cohort by Male Pattern Baldness

Characteristic	No Baldness		Any Baldness								
			Frontal Baldness Only		Frontal Plus Any Vertex Baldness						
					Frontal Plus Mild Vertex Baldness		Frontal Plus Moderate Vertex Baldness		Frontal Plus Severe Vertex Baldness		
	No.	%	No.	%	No.	%	No.	%	No.	%	*P**
Event status											.368
Censored	17,678	46.6	9,411	24.8	4,760	12.5	3,643	9.6	2,440	6.4	
Event	522	45.9	279	24.5	142	12.5	129	11.3	66	5.8	
Randomly assigned group											.899
Usual care	8,750	46.7	4,659	24.9	2,332	12.5	1,785	9.5	1,198	6.4	
Intervention	9,450	46.4	5,031	24.7	2,570	12.6	1,987	9.8	1,308	6.4	
Age at SQX, years											< .001
< 65	2,569	46.4	1,301	23.5	796	14.4	517	9.3	356	6.4	
65-69	5,288	46.5	2,782	24.5	1,456	12.8	1,108	9.7	739	6.5	
70-74	4,829	47.3	2,487	24.3	1,286	12.6	971	9.5	642	6.3	
≥ 75	5,514	46.2	3,120	26.1	1,364	11.4	1,176	9.8	769	6.4	
Education											.057
Less than high school	1,066	47.3	564	25.0	256	11.3	215	9.5	155	6.9	
High school graduate	5,402	46.6	2,932	25.3	1,400	12.1	1,095	9.5	756	6.5	
Some college	3,655	46.9	1,941	24.9	930	11.9	765	9.8	495	6.4	
College graduate	3,708	47.1	1,930	24.5	1,010	12.8	737	9.4	488	6.2	
Postgraduate	4,326	45.6	2,302	24.3	1,292	13.6	950	10.0	608	6.4	
Marital status											.352
Married or cohabiting	14,867	46.7	7,931	24.9	3,967	12.4	3,048	9.6	2,053	6.4	
Single†	3,200	46.6	1,668	24.3	895	13.0	688	10.0	421	6.1	
Race											< .001
White	15,874	45.5	8,816	25.3	4,440	12.7	3,448	9.9	2,316	6.6	
Black	483	55.2	172	19.7	116	13.3	61	7.0	43	4.9	
Other‡	1,110	64.3	324	18.8	160	9.3	99	5.7	34	2.0	
First-degree relative(s) had prostate cancer											.548
No	14,463	46.7	7,687	24.8	3,890	12.6	2,958	9.5	1,984	6.4	
Yes	1,560	45.4	863	25.1	440	12.8	353	10.3	219	6.4	
Diabetes											.541
No	13,274	46.7	7,064	24.8	3,586	12.6	2,740	9.6	1,784	6.3	
Yes	2,947	46.3	1,566	24.6	788	12.4	643	10.1	426	6.7	
Myocardial infarction											< .001
No	13,633	47.0	7,195	24.8	3,636	12.5	2,779	9.6	1,769	6.1	
Yes	2,438	44.6	1,373	25.1	678	12.4	570	10.4	413	7.5	
Enlarged prostate											< .001
No	10,109	47.6	5,200	24.5	2,598	12.2	1,990	9.4	1,323	6.2	
Yes	7,946	45.4	4,410	25.2	2,255	12.9	1,746	10.0	1,151	6.6	
BMI at age 50 years, kg/m^2											< .001
< 25.0	6,023	47.3	3,275	25.7	1,534	12.1	1,191	9.4	698	5.5	
25.0-29.9	8,069	45.9	4,354	24.8	2,289	13.0	1,709	9.7	1,142	6.5	
≥ 30	2,506	46.5	1,245	23.1	682	12.6	550	10.2	410	7.6	
Cigarette smoking											< .001
Never	6,027	44.8	3,290	24.5	1,780	13.2	1,378	10.3	966	7.2	
Ever	11,659	47.7	6,083	24.9	2,984	12.2	2,251	9.2	1,453	5.9	
Aspirin use frequency											.001
None or < 1 time per month	5,719	48.0	2,967	24.9	1,434	12.0	1,083	9.1	706	5.9	
2 times per week or less	1,756	46.4	924	24.4	492	13.0	383	10.1	226	6.0	
3-6 times per week	1,820	45.4	1,050	26.2	502	12.5	372	9.3	264	6.6	
≥ 7 times per week	8,492	45.9	4,530	24.5	2,363	12.8	1,860	10.1	1,239	6.7	

Abbreviations: BMI, body mass index; SQX, supplemental questionnaire.
*P values were calculated from χ^2 tests for nonmissing categorical variables with controls without prostate cancer as the comparison group.
†Single includes widowed, divorced, separated, and never married.
‡Other race includes Asian, Native Hawaiian or other Pacific Islander, American Indian, or Alaskan Native.

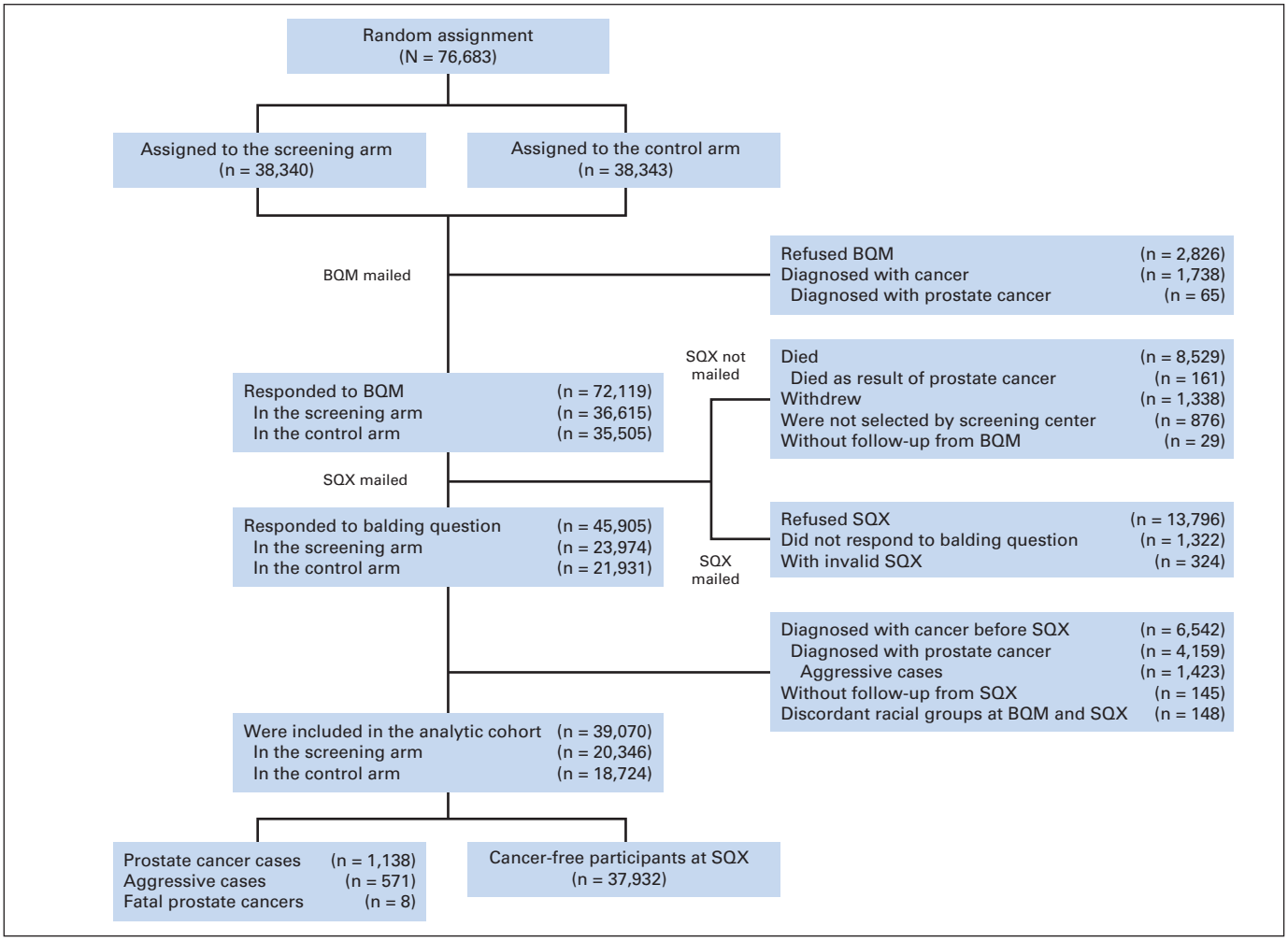

Fig A1. Flow diagram showing how the analytic cohort was determined from participants in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. BQM, baseline questionnaire–men; SQX, supplemental questionnaire.