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Original Article

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SLCO1B3 and *SLCO2B1* genotypes, androgen deprivation therapy, and prostate cancer outcomes: a prospective cohort study and meta-analysis

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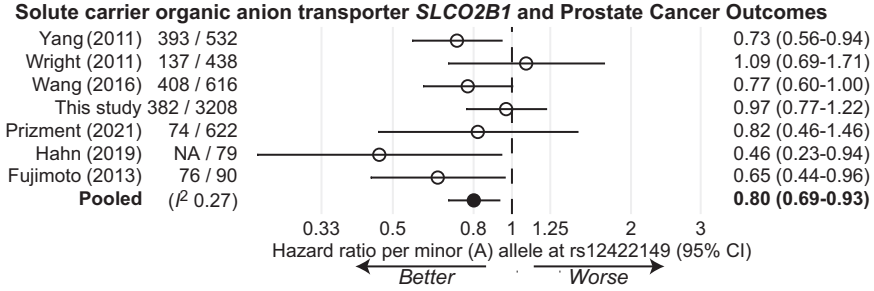
Abstract

Solute carrier organic anion (SLCO) transporters (OATP transporters) are involved in cellular uptake of drugs and hormones. Germline variants in *SLCO1B3* and *SLCO2B1* have been implicated in prostate cancer progression and therapy response, including to androgen deprivation and statin medications, but results have appeared heterogeneous. We conducted a cohort study of five single-nucleotide polymorphisms (SNPs) in *SLCO1B3* and *SLCO2B1* with prior evidence among 3208 men with prostate cancer who participated in the Health Professionals Follow-up Study or the Physicians' Health Study, following participants prospectively after diagnosis over 32 years (median, 14 years) for development of metastases and cancer-specific death (lethal disease, 382 events). Results were suggestive of, but not conclusive for, associations between some SNPs and lethal disease and differences by androgen deprivation and statin use. All candidate SNPs were associated with *SLCO* mRNA expression in tumor-adjacent prostate tissue. We also conducted a systematic review and harmonized estimates for a dose-response meta-analysis of all available data, including 9 further studies, for a total of 5598 patients and 1473 clinical events. The A allele of the exonic SNP rs12422149 (14% prevalence), which leads to lower cellular testosterone precursor uptake via SLCO2B1, was associated with lower rates of prostate cancer progression (hazard ratio per A allele, 0.80; 95% confidence interval, 0.69–0.93), with little heterogeneity between studies (I^2, 0.27). Collectively, the totality of evidence suggests a strong association between inherited genetic variation in *SLCO2B1* and prostate cancer prognosis, with potential clinical use in risk stratification related to androgen deprivation therapy.

Graphical Abstract



Abbreviations: ADT, androgen deprivation therapy; eQTL, expression quantitative trait loci; PHS, Physicians' Health Study; SLCO, solute carrier organic anion transporter; SNPs, single-nucleotide polymorphisms.

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Introduction

Solute carrier organic anion transporters (SLCO) are cell membrane proteins that mediate cellular uptake of certain steroids and drugs (1–3). This function has been suggested to be particularly relevant in hormone-dependent cancers, such as breast and prostate cancer, where hormone transport can be a rate-limiting step of cell growth and cancer progression. *In vitro* studies have found SLCO transporters to be involved in uptake of testosterone (4) and its precursor dehydroepiandrosterone (DHEAS) (5,6), as well as the extragonadal androgen synthesis inhibitor abiraterone acetate (7,8). Additionally, cholesterol-lowering statin medications, at least at supraphysiologic concentrations in cell lines, may impair SLCO-mediated uptake of DHEAS (9).

Germline variants in *SLCO* genes may affect expression and function of the SLCO transporters. Clinically, most previous studies on *SLCO* single-nucleotide polymorphisms (SNPs) and outcomes after prostate cancer diagnosis had limited precision, particularly for clinically relevant outcomes such as metastases and death from prostate cancer (lethal disease) among men initially diagnosed with non-metastatic disease. Moreover, to what extent previously reported results are consistent with each other has been challenging to understand because genotype coding varied widely.

Here, we report results from a prospective cohort study with long-term follow-up for lethal prostate cancer and with information on androgen deprivation therapy (ADT) and statin use. We also undertook a systematic review and meta-analysis, consolidating all available data on SNPs in *SLCO2B1* (also referred to as OATP2B1) and *SLCO1B3* (OATP1B3) and prostate cancer outcomes.

Methods

Cohort study

The cohort study included men who were diagnosed with prostate cancer while being participants of two prospective cohort studies, the Health Professionals Follow-up Study (HPFS) and the Physicians' Health Study (PHS). The HPFS enrolled 51 529 male health professionals from all 50 US states who were 40–75 years old in 1986, with detailed follow-up through biennial questionnaires (10). The PHS was a randomized controlled trial of aspirin and vitamin supplements for cancer and cardiovascular prevention, enrolling 22 071 male physicians 40–84 years old in 1982 (11), later followed as a prospective cohort.

New cancer diagnoses reported by the medical professionals in both cohorts were verified and patients were prospectively followed through detailed biennial questionnaires, contact to treating physicians, systematic review of medical records (including for development of metastases), and detailed ascertainment of death causes. The research was approved by institutional review boards at Harvard T.H. Chan School of Public Health, Mass General Brigham, and those of participating registries as required, with written informed consent provided at cohort enrollment.

Genotyping from both cohorts was based on previous nested case-control studies, with merging by genotyping platform and imputation to 1000 Genomes Phase 1 as the reference panel described previously (12). SNPs of interest were selected from two prior studies (5,6), which correspond to SNPs assessed in the meta-analysis (see below). We assessed for linkage disequilibrium with Pearson correlations.

For an expression quantitative trait loci (eQTL) analysis, we assessed a substudy with transcriptomic data generated on formal-fixed paraffin-embedded tumor tissue from men treated with prostatectomy or transurethral resection of the prostate that was obtained from treating hospitals, centrally re-reviewed, and re-graded, as described previously (13). Whole-transcriptome expression profiling using the Affymetrix GeneChip Human Gene 1.0 ST array (Gene Expression Omnibus: GSE62872) was performed in an extreme case-control study, contrasting lethal tumors with those of men who remained metastasis-free for at least 8 years, including tumor-adjacent histologically normal-appearing tissue in a subset of cases, as described previously (14,15). We estimated ratios of mean expression (*SLCO1B3* or *SLCO2B1*) per minor allele for each SNP using a generalized linear regression model with a log link; similar analyses were done per Gleason score in ordinal grade groups. We assessed the association between *SLCO1B3* and *SLCO2B1* mRNA expression and lethal disease using univariable logistic regression.

To assess the association of each SNP and lethal prostate cancer among men initially diagnosed with non-metastatic prostate cancer, participants were followed from diagnosis or DNA sampling (if after diagnosis) to development of distant metastases, death from prostate cancer, death from any cause, or end of follow-up for this analysis (HPFS: January 2019, PHS: January 2015). For ADT, of which many prescriptions are after onset of metastases, a sensitivity analysis examined fatal prostate cancer outcome, following participants beyond the metastasis date. Hazard ratios (HRs) per categorical genotype, with homozygotes for the major allele as the reference, were estimated using Cox proportional hazards regression. We addressed population stratification by restricting analyses to men of self-reported White race and adjustment for the first three principal components of genetic variation; we additionally adjusted for age at cancer diagnosis, calendar year of diagnosis, and genotyping platform to sufficiently account for different selection mechanisms (16). For comparability with other studies, complementary analyses used additive coding per one additional minor allele.

To assess to what extent effects of genotype were modified by statin use or by treatment with ADT, person-time of HPFS participants was stratified by therapy for analyses of potential effect measure modification on the multiplicative scale. We considered men as castrate for 6 months beyond the reported end date of ADT (17). We imputed dates when the exact start and stop dates of ADT were unknown as follows: we considered men castrate throughout follow-up if primary therapy was orchidectomy or hormonal therapy in absence of other primary or secondary therapy; if ADT was (neo-) adjuvant therapy, we assumed it to have stopped by 1 year after diagnosis; and if ADT was initiated >1 year after diagnosis, we assumed continuous exposure for the remainder of follow-up. We report HRs from jointly classifying men by genotype and treatment, HRs per additively coded genotype from treatment-stratified models, and relative HRs, i.e. the exponentiated coefficients from interaction terms between additively coded genotype and therapy from unstratified models.

Systematic review and meta-analysis

PubMed/MEDLINE and EMBASE databases were systematically queried by a reference librarian (K.M.) without date, language, or publication type restrictions (see Supplementary Appendix, available at *Carcinogenesis* Online for details). Studies were required to have studied men; have genotyped SNPs in or related to *SLCO1B3* or *SLCO2B1*; assessed any longitudinal outcome related to prostate cancer and/or overall survival; and provided estimates of effect size and variance. One study that provided *P*-values only (18) was not included. Two independent reviewers screened titles and abstracts of the full search up to 20 December 2020, evaluated full text, and extracted study data in parallel, including allele groupings and corresponding HRs for each study, outcome, and SNP. An interval screening of titles, abstracts, and full text of PubMed results by 11 November 2022 did not identify additional studies that met inclusion criteria.

For comparability between studies, we re-calculated estimates as the HR per each additional minor allele (additive coding). First, we assigned the count of minor alleles to each reported genotype category. For example, for rs12422149 with major allele G and minor allele A, a genotype of GG (homozygous major allele) corresponded to 0 minor alleles, a genotype of GA to 1 minor allele, and AA to 2 minor alleles. Coding was reversed for studies that treated the minor allele as the reference (HR, 1) and the major allele as the risk allele. If a study reported homozygotes for the major allele (e.g. GG) as one category and heterozygotes plus homozygotes for the minor allele combined in one estimate (e.g. GA/AA combined), we considered the latter estimate a weighted average of the two genotypes (here, GA and AA). To assign a count of minor alleles to this weighted average, we estimated the proportion of heterozygotes (here, GA) and of homozygotes for the minor allele (here, AA) under the Hardy-Weinberg equilibrium. With the count of homozygotes for the major allele given by $f(\mathrm{GG}) = p^2$ and the combined category $f(\mathrm{GA}) + f(\mathrm{AA}) = 2pq + q^2$, we estimated $p = \sqrt{f(GG)}$ and, solving the quadratic equation, $q = \frac{2p+\sqrt{4p^2+4(f(\mathrm{GA})+f(\mathrm{AA}))}}{2}$ and then the minor allele dosage for GA/AA as $1 + \frac{q^2}{2pq}$. For example, if $f(\mathrm{GG}) = 424$ and $f(\mathrm{GA}) + f(\mathrm{AA}) = 98$ as for rs12422149 in (5), then $p = \sqrt{424}$ and $q = 2.23$, $f(\mathrm{GA}) = 2pq = 98$ and $f(\mathrm{AA}) = q^2 = 5$. Thus, GA/AA corresponds to $1 + \frac{5}{98} = 1.05$ minor alleles.

Second, to transform the reported HR into an HR per one minor allele, we used fixed-effects dose-response meta-analysis within each study, SNP, and outcome. We implemented this model in the dosresmeta package version 2.1.1 (19) with the Greenland-Longnecker approach to handling the covariance for studies that reported estimates for all three genotypes and per-genotype participant counts and reconstructed variances if event counts were not reported (20).

Third, we performed dose-response meta-analyses with random study effects to obtain pooled estimates across all studies reporting on a SNP and outcome type (prostate cancer progression outcomes; overall survival). Overall, our approach corresponded to a two-stage dose-response meta-analysis.

Results

Study population of the prospective cohort study

The prospective cohort study included 3208 men with non-metastatic prostate cancer,of which 96% had clinically localized disease (Table 1). Only 6% of participants were treated with primary hormonal therapy, but a total of 694 participants (29% of participants from HPFS) received ADT over at least part of the disease course. Among 2420 participants of HPFS, 849 (35%) were statin users at cancer diagnosis, who tended to be diagnosed in more recent calendar years at an older age. Statin use was not recorded among 17 HPFS participants and all 788 participants from PHS.

Genotyping quality was acceptable for all six SNPs, without statistical evidence against the Hardy-Weinberg equilibrium ($0.07 \le P \le 0.65$). However, the *SLCO1B3* SNPs rs7311358 and rs4149117 were in perfect linkage disequilibrium (Pearson $r = 1$; Supplementary Figure 1, available at *Carcinogenesis* Online), and rs7311358 was excluded from analyses.

SLCO1B3 and SLCO2B1 mRNA expression in a nested transcriptome study

Absolute expression levels of both genes in prostate tumor tissue ($n = 420$) were low, with median *SLCO1B3* expression ranking at the lower 1st percentile of median gene-level expression among all 22 256 genes measured, and *SLCO2B1* ranking at the lower 35th percentile. In an eQTL analysis, each minor allele was associated with 3–5% higher mean *SLCO1B3* or *SLCO2B1* mRNA expression in tumor-adjacent, histologically normal-appearing tissue ($n = 158$); associations in tumor tissue ($n = 262$) were inconclusive (Supplementary Figure 2, available at *Carcinogenesis* Online; Supplementary Table 1, available at *Carcinogenesis* Online).

Neither Gleason scores (Supplementary Figure 3, available at *Carcinogenesis* Online) nor statin use (Supplementary Figure 4, available at *Carcinogenesis* Online) were associated with *SLCO1B3* or *SLCO2B1* expression. Tumor expression of neither gene was associated with long-term risk of lethal disease (Supplementary Table 2, available at *Carcinogenesis* Online).

Genotypes and lethal disease in the prospective cohort study

With 41 261 person-years of follow-up over up to 32 years per participant (median 14.3 years; interquartile range 9.9–18.4), we documented 382 lethal events. Overall, we observed no clear associations between any of the five SNPs and rates of lethal disease (Table 2). *SLCO2B1* SNP rs1077858 had the strongest association (HR 1.14 per minor allele, 95% CI 0.98–1.33).

To what extent statin use-modified associations between genotypes and lethal disease differed was not clear from our results, given the relatively wide CIs around the estimates. We observed potentially slightly stronger associations between variation at certain SNPs and lethal disease among statin users after cancer diagnosis than non-users (ratio of HRs per minor allele for rs1789693 1.31, 95% CI 0.84–2.05; ratio of HRs for rs949069 1.12, 95% CI 0.69–1.81; Table 3). Differences appeared more pronounced when comparing by statin use at diagnosis (ratio of HRs, compared with non-users, for rs1789693 1.45, 95% CI 0.90–2.33; ratio of HRs for rs949069 1.80, 95% CI 1.10–2.93; Supplementary Table 3, available at *Carcinogenesis* Online).

Similarly, we observed potential modest differences in associations between genotypes and lethal disease by ADT

Table 1. Characteristics of men diagnosed with primary, non-metastatic prostate cancer during prospective follow-up of the Health Professionals Follow-up Study (HPFS, 1993–2017) and Physicians' Health Study (PHS, 1982–2010) cohorts, by statin use versus non-use at diagnosis (available in HPFS only) versus no available statin data (in PHS and among 17 HPFS participants)

Characteristic[a]	Overall	By statin use at cancer diagnosis		
		Statin non-user	Statin user	No statin data
N	3208	1554	849	805
Cohort				
HPFS	2420 (75%)	1554 (100%)	849 (100%)	17 (2%)
PHS	788 (25%)	0 (0%)	0 (0%)	788 (98%)
Family history of prostate cancer	735 (24%)	329 (21%)	171 (20%)	235 (36%)
Unknown	148	0	0	148
Age at diagnosis [years]	70 (65, 75)	69 (64, 75)	72 (67, 77)	70 (65, 75)
Year of diagnosis	2000 (1996, 2004)	2000 (1996, 2004)	2004 (2001, 2007)	1995 (1991, 1999)
Gleason score				
5–6	1388 (49%)	698 (50%)	368 (49%)	322 (47%)
3 + 4	649 (23%)	333 (24%)	180 (24%)	136 (20%)
4 + 3	342 (12%)	171 (12%)	96 (13%)	75 (11%)
8	250 (9%)	96 (7%)	56 (7%)	98 (14%)
9–10	201 (7%)	88 (6%)	55 (7%)	58 (8%)
Unknown	378	168	94	116
Clinical stage				
T1/T2	2801 (96%)	1369 (97%)	747 (98%)	685 (93%)
T3	86 (3%)	29 (2%)	16 (2%)	41 (6%)
T4/N1	19 (1%)	11 (1%)	0 (0%)	8 (1%)
Unknown	302	145	86	71
PSA at diagnosis [ng/ml]	7 (5, 10)	7 (5, 10)	6 (5, 9)	7 (5, 12)
Unknown	452	169	92	191
Primary treatment				
Prostatectomy	1363 (47%)	697 (50%)	286 (38%)	380 (52%)
Radiation	1053 (36%)	480 (34%)	342 (45%)	231 (32%)
Hormonal therapy only	175 (6%)	66 (5%)	45 (6%)	63 (9%)
Other	480 (17%)	231 (16%)	133 (17%)	116 (16%)
Unknown	312	146	88	78

[a]Median (interquartile range) or count (percent).

treatment (rs1789693; Table 4). For the outcome of fatal prostate cancer (230 events over 30 928 person-years of follow-up in HPFS), associations for rs1789693 were similar by ADT treatment, but associations for rs4149117 appeared to potentially differ (Supplementary Table 4, available at *Carcinogenesis* Online).

Systematic review

The systematic literature search yielded 569 publications following duplicate removal. After review of titles, abstracts, and full text, 10 studies were included in the meta-analysis, including this cohort study (Supplementary Figure 5, available at *Carcinogenesis* Online) (4–6,21–26). Seven studies were hospital-based cohort studies of men typically with advanced/metastatic prostate cancer who were all probably treated with ADT from start of follow-up (Table 5) (4–6,21,22,24,26). Two studies were population-based (23,25) and included men mostly with primary disease at the start of follow-up, as in our cohort study, and a subset of men received ADT during follow-up.

Beyond *SLCO* genotype data summarized in our meta-analysis, two studies additionally reported data on tumor *SLCO2B1* or *SLCO1B3* mRNA expression (6,25). One study reported immunofluorescence staining for SLCO1B3 (4).

Meta-analysis

Of the seven unique SNPs reported on in the 10 studies, estimates for 5 SNPs (the same as in our prospective cohort study) were available from more than one study and were included in the meta-analysis. Prostate cancer-related outcomes, including biochemical recurrence, metastasis, radiographic progression, castration resistance, and death from prostate cancer, were reported by 7 studies (1473 events among 5598 men; Table 5; Supplementary Table 5, available at *Carcinogenesis* Online); overall survival was an outcome in 5 studies (>1031 events among 2444 men).

The minor allele in rs12422149 was associated with lower rates of prostate cancer outcomes (HR per A allele 0.80, 95% CI 0.69–0.93; Figure 1), based on 7 studies with little between-study heterogeneity (I^2 27%). This pooled estimate

Table 2. *SLCO2B1* and *SLCO1B3* genotypes and rates of progression to lethal prostate cancer (metastases/prostate cancer death) among men with primary, non-metastatic prostate cancer in the HPFS (1993–2019) and PHS (1982–2014)

SNP	No risk allele[a]	Heterozygous[a]	Homozygous[a]	Per risk allele[b]
SLCO2B1				
rs12422149	GG	GA	AA	
	307/33 204	72/7541	3/516	
	1 (reference)	1.02 (0.79–1.32)	0.59 (0.19–1.83)	0.96 (0.76–1.22)
rs1789693	AA	AT	TT	
	183/18 539	155/17 686	44/5036	
	1 (reference)	0.87 (0.70–1.08)	0.86 (0.62–1.20)	0.96 (0.81–1.14)
rs1077858	AA	AG	GG	
	160/17 778	158/18 592	64/4,891	
	1 (reference)	1.00 (0.80–1.25)	1.43 (1.07–1.92)	1.14 (0.98–1.33)
rs949069	GG	GA	AA	
	248/24 872	111/14 294	23/2095	
	1 (reference)	0.78 (0.62–0.98)	1.11 (0.72–1.70)	0.90 (0.75–1.07)
SLCO1B3				
rs4149117	GG	GT	TT	
	284/31 110	94/9369	4/781	
	1 (reference)	1.11 (0.88–1.40)	0.59 (0.22–1.59)	1.02 (0.83–1.26)

[a]Genotype, lethal events/person-years, and hazard ratio (95% CI), adjusted for age at diagnosis, year of diagnosis, genotyping platform, and the first three principal components of genetic ancestry.
[b]Adjusted hazard ratio (95% CI) with additively coded genotypes, per risk allele.

was not sensitive to any single study in a leave-one-out analysis (Supplementary Figure 6, available at *Carcinogenesis* Online). The HR per minor (G) allele in rs1077858 of 1.14 (95% CI 0.99–1.30) was based on only three studies with substantial heterogeneity (I^2 68%). Associations with prostate cancer outcomes were null for the two other SNP in *SLCO2B1*, including rs1789693 (HR per T allele 1.03, 95% CI 0.92–1.15, 5 studies), with noticeable between-study heterogeneity (I^2 0.47), and null for rs4149117, the one SNP in *SLCO1B3*, without heterogeneity.

For overall survival (Supplementary Figure 7, available at *Carcinogenesis* Online), the association for rs12422149 was close to null (HR per A allele 0.95, 95% CI 0.82–1.10; 3 studies with I^2 0%), while the minor allele at rs1789693 was associated with lower mortality rates (HR per T allele 0.88, 95% CI 0.81–0.96), based on 3 studies (I^2 24%).

Discussion

In a prospective cohort study as well as a systematic review and meta-analysis, we assessed inherited genetic variation in SLCO transporters genes as predictors of outcomes among men with prostate cancer. A noticeable finding, with evidence from 7 studies, is a 20% lower rate (95% CI 7–31%) of prostate cancer outcomes per A allele at rs12422149, the minor allele that has a prevalence of 14% and that was shown previously to lead to lower cellular DHEAS uptake via SLCO2B1, androgen receptor activation, and cell proliferation (5). Associations at other loci were more heterogeneous between studies; for rs1789693, associations with overall survival based were inconsistent with and not explained by results for prostate cancer outcomes.

An obvious characteristic of the meta-analysis presented here, and other meta-analyses, is that clinically different patient populations and clinical outcomes are being combined, as few of the studies included had similar inclusion criteria or outcome definitions (Table 5). The observation that germline variation at rs12422149 was associated with prostate cancer outcomes despite this substantial clinical heterogeneity could be regarded as support for the robustness of this finding. The meta-analytic result was also robust to the exclusion of any single of the 7 studies reporting on rs12422149. While estimates from our prospective cohort study were null, they are statistically compatible with the pooled estimate. Importantly, SLCO2B1 has been implicated in cellular androgen uptake, a process that is relevant across the disease course. We thus attempted to disentangle to what extent a potential impact of germline variation in the two *SLCO* genes would be specific to times when patients were treated with ADT. Interestingly, while statistical evidence for effect modification by ADT was weak, the estimates of our prospective cohort study per risk allele at rs12422149 among ADT-treated participants (HR 0.83, 95% 0.49–1.41 for lethal disease, Table 4; HR 0.68, 95% CI 0.38–1.24 for fatal disease, Supplementary Table 4, available at *Carcinogenesis* Online) were similar to the pooled estimate from the meta-analysis (HR 0.80, 95% CI 0.69–0.93), which was dominated by studies among ADT-treated patients.

We also explored if potential effects on lethal prostate cancer could be modified through use of statins, which have been suggested *in vitro* to inhibit androgen uptake (9). The purpose of these analyses was to assess the extent to which associations of statin use with prognosis may differ by genotype, not an estimation of overall statin effects, which would need to take additional measures to address confounding. Our results were compatible with modest differences by statin use but inconclusive because of limited precision. Substantially larger samples sizes would be needed to assess if effects of statins differ by *SLCO* genotype. Data on statin type and dosage would be useful as well. Except our cohort study, none

Table 3. *SLCO2B1* and *SLCO1B3* genotypes and rates of progression to lethal prostate cancer (metastases/prostate cancer death) among men with primary, non-metastatic prostate cancer in the HPFS (1993–2019), by statin use after cancer diagnosis (time-varying)

SNP	Statin	No risk allele[a]	Heterozygous[a]	Homozygous[a]	Per risk allele[b]	Interaction[c]
SLCO2B1						
rs12422149	Non-users	GG	GA	AA		
		118/13 952	26/3027	0/228		
		1 (reference)	1.08 (0.70–1.65)	—	0.98 (0.65–1.45)	
	Users	72/9884	14/2298	1/128		
		0.94 (0.70–1.28)	0.82 (0.47–1.44)	1.02 (0.14–7.33)	0.93 (0.55–1.57)	0.96 (0.50–1.84)
rs1789693	Non-users	AA	AT	TT		
		70/7833	56/7311	18/2064		
		1 (reference)	0.84 (0.59–1.19)	0.98 (0.58–1.64)	0.97 (0.74–1.29)	
	Users	33/5328	45/5537	9/1445		
		0.74 (0.49–1.13)	0.99 (0.67–1.45)	0.76 (0.38–1.54)	1.25 (0.88–1.76)	1.31 (0.84–2.05)
rs1077858	Non-users	AA	AG	GG		
		65/7656	55/7536	24/2015		
		1 (reference)	0.90 (0.63–1.30)	1.29 (0.80–2.06)	1.04 (0.82–1.32)	
	Users	32/5048	40/5684	15/1577		
		0.82 (0.53–1.26)	0.91 (0.61–1.36)	1.27 (0.72–2.24)	1.26 (0.92–1.74)	1.16 (0.78–1.72)
rs949069	Non-users	GG	GA	AA		
		101/10547	34/5826	9/834		
		1 (reference)	0.62 (0.42–0.91)	1.22 (0.62–2.43)	0.80 (0.59–1.09)	
	Users	56/7296	26/4423	5/591		
		0.88 (0.63–1.23)	0.67 (0.43–1.04)	1.13 (0.46–2.80)	0.95 (0.65–1.39)	1.12 (0.69–1.81)
SLCO1B3						
rs4149117	Non-users	GG	GT	TT		
		112/12 875	31/3967	1/365		
		1 (reference)	0.94 (0.63–1.41)	0.34 (0.05–2.43)	0.89 (0.62–1.28)	
	Users	68/9490	18/2674	1/145		
		0.91 (0.67–1.24)	0.85 (0.52–1.41)	0.81 (0.11–5.80)	0.91 (0.57–1.47)	1.09 (0.60–1.97)

[a]Genotype, lethal events/person-years, and hazard ratio (95% CI), adjusted for age at diagnosis, year of diagnosis, genotyping platform, and the first three principal components of genetic ancestry.
[b]Hazard ratio (95% CI) with additively coded genotypes, per risk allele, from models stratified by time-varying post-diagnosis statin use.
[c]Relative hazard ratio (95% CI) for multiplicative effect measure modification between additively coded genotype ("Per risk allele") and time-varying post-diagnosis statin use.

of the other studies included in the meta-analysis had assessed effect modification by ADT or statin use.

Experimental studies have demonstrated effects of *SLCO2B1* SNPs rs12422149 (5) and rs1077858 (6) on androgen uptake. In addition, experimental studies have also suggested that SNPs influence mRNA expression of *SLCO1B3* (4) and *SLCO2B1* (5,6). Our eQTL analyses corroborate these findings at least in tumor-adjacent histologically normal-appearing prostate tissue. Results in tumor tissue were inconclusive, possibly because of complex other oncogenic signaling that alters gene expression in a tumor beyond germline variants. Absolute expression levels detected by our microarray were low, as observed in another study (27), which hampered our ability to assess differences in *SLCO2B1* and *SLCO1B3* gene expression by tumor grade, statin use, or in relation to prognosis. Differences in *SLCO2B1* expression by Gleason grade (28) and associated with ADT have been observed (29). Higher *SLCO2B1* mRNA expression, as measured by RNA sequencing, was associated with higher rates of biochemical recurrence in The Cancer Genome Atlas (28).

The prospective cohort study and the meta-analysis were larger than any individual previous study. However, with the relatively low number of studies per SNP and outcome, we were unable to assess important aspects of effect modification, e.g. if associations differed between the population-based cohort studies that mainly included men early in their disease course and the hospital-based studies of men late in their disease course.

Our findings may be limited in generalizability and transportability. Most of the studies in the meta-analysis controlled for self-reported race, usually through restriction of study populations, and thus reduced confounding by ancestry (population stratification). Only one other study adjusted for principal components of genetic variation, which may be relevant even within the group of European-ancestry men, given differences in risk of lethal prostate cancer by ancestry within Europe (30). To what extent findings are generalizable to other racial and ethnic groups is unknown; the risk allele at rs12422149 appears to have similar prevalence in African populations and possibly higher prevalence in Asian populations (31).

Of note, our prospective cohort study and the meta-analysis addressed how germline genetic variation in SLCO transporters is associated with prognosis among men already

Table 4. *SLCO2B1* and *SLCO1B3* genotypes and rates of progression to lethal prostate cancer (metastases/prostate cancer death) among men with primary, non-metastatic prostate cancer in the HPFS (1993–2019), by androgen deprivation therapy (time-varying)

SNP	ADT	No risk allele[a]	Heterozygous[a]	Homozygous[a]	Per risk allele[b]	Interaction[c]
SLCO2B1						
rs12422149	No ADT	GG	GA	AA		
		244/30 645	54/6849	3/496		
		1 (reference)	0.99 (0.73–1.33)	0.68 (0.22–2.13)	0.94 (0.72–1.22)	
	ADT-treated	69/2776	18/875	0/20		
		2.55 (1.94–3.35)	2.25 (1.39–3.65)	—	0.83 (0.49–1.41)	0.92 (0.51–1.64)
rs1789693	No ADT	AA	AT	TT		
		151/17 041	117/16 311	33/4637		
		1 (reference)	0.80 (0.63–1.02)	0.78 (0.53–1.14)	0.89 (0.73–1.08)	
	ADT-treated	33/1712	42/1513	12/447		
		1.88 (1.28–2.74)	2.45 (1.73–3.48)	2.58 (1.43–4.67)	1.38 (0.99–1.92)	1.48 (1.01–2.18)
rs1077858	No ADT	AA	AG	GG		
		127/16 475	124/16 999	50/4516		
		1 (reference)	0.99 (0.78–1.27)	1.40 (1.01–1.95)	1.13 (0.96–1.34)	
	ADT-treated	35/1446	38/1796	14/430		
		2.44 (1.67–3.57)	2.48 (1.72–3.58)	3.86 (2.21–6.74)	1.06 (0.77–1.48)	1.03 (0.71–1.48)
rs949069	No ADT	GG	GA	AA		
		195/22 938	89/13 128	17/1924		
		1 (reference)	0.79 (0.62–1.02)	1.06 (0.64–1.74)	0.90 (0.73–1.10)	
	ADT-treated	56/2108	25/1377	6/186		
		2.51 (1.85–3.40)	1.93 (1.27–2.93)	2.85 (1.24–6.52)	0.90 (0.62–1.32)	1.01 (0.67–1.53)
SLCO1B3						
rs4149117	No ADT	GG	GT	TT		
		224/28 674	73/8568	4/748		
		1 (reference)	1.10 (0.84–1.43)	0.70 (0.26–1.89)	1.04 (0.82–1.31)	
	ADT-treated	63/2761	24/877	0/34		
		2.44 (1.83–3.24)	2.95 (1.93–4.51)	—	1.08 (0.68–1.72)	1.07 (0.65–1.79)

[a]Genotype, lethal events/person-years, and hazard ratio (95% CI), adjusted for age at diagnosis, year of diagnosis, genotyping platform, and the first three principal components of genetic ancestry.
[b]Hazard ratio (95% CI) with additively coded genotypes, per risk allele, from models stratified by time-varying post-diagnosis androgen deprivation therapy.
[c]Relative hazard ratio (95% CI) for multiplicative effect measure modification between additively coded genotype ("Per risk allele") and time-varying post-diagnosis androgen deprivation therapy.

diagnosed with prostate cancer. Neither assess the association of these variants with risk of prostate cancer among initially cancer-free men. Such a study design would address the possibility that *SLCO* variants may also alter risk of developing (or being diagnosed with) prostate cancer, rather than its progression after diagnosis. Finally, many variants of androgen receptor-targeted therapy exist that we had to consider jointly. It is possible that ADT efficacy could be more profoundly affected by *SLCO2B1* variants that alter DHEAS uptake efficacy than might be the efficacy of more potent suppressors of androgen production, such as abiraterone acetate. At the same time, it is also possible that scavenger effects would become particularly important in the latter setting. Additional research beyond one study included in our meta-analysis (22) and one additional study published in the interim (32) will be needed.

In summary, the meta-analysis presented here provides evidence that some inherited genetic variation in *SLCO2B1* is quite strongly associated with prognosis after a prostate cancer diagnosis and supports a biologic role of these variants or at least related variants in linkage disequilibrium. Key to these insights was harmonization and pooling of genotype summary results from smaller studies, including the prospective study reported here, that individually had imprecise estimates and appeared heterogeneous merely due to genotype coding choices. Replication of our findings through large consortia of individual-level data would be key, also to further assess whether these polymorphisms may indicate sensitivity to ADT and statin use, as assessed in our cohort study. Finally, *SLCO2B1* rs12422149 and other variants could be assessed as one component of clinical risk stratification in recently reported phase 3 randomized controlled trials that tested early use of novel androgen receptor-targeted therapies in advanced prostate cancer.

Supplementary material

Supplementary data are available at *Carcinogenesis* online.

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Table 5. Characteristics of studies included in the meta-analysis[a]

Study, Year	Study base	Cancer state at inclusion	Patients (*N*)[b]	ADT (%)	White[c] (%)	Follow-up[d]	Outcome(s) (events)
Hamada, 2008 (4)	Hospital	Castration-resistant	180	100	100	NR	Overall survival (NR)
Yang, 2011 (5)	Hospital	ADT start (49% metastatic)	538	100	95	5.1	PSA progression or start of secondary hormone therapy (393)
Fujimoto, 2013 (21)	Hospital	ADT start	87	100	0	3.3	Castration resistance (76), Overall survival (53)
Wang, 2016 (6)	Hospital	Start of ADT (58% metastatic)	616	100	NR	4.2[e]	PSA progression or start of secondary hormonal therapy (408), overall mortality (537)
Kohli, 2013 (26,34)[f]	Hospital	Metastatic castration-resistant	240	100	97	3.2	Overall survival (144)
Tripathi, 2018 (24)	Hospital	Metastatic castration-resistant	289	100	NR	NR	Overall survival (NR)
Hahn, 2019 (22)	Hospital	Metastatic castration-resistant, on abiraterone	79	100	NR	NR	PSA, radiographic, or clinical progression (NR)
Wright, 2011 (25)	Population	Primary prostate cancer	469	5[g]	100	8.9	PSA progression or recurrence (143) Prostate cancer mortality (66)
Prizment, 2021 (23)	Population	Primary prostate cancer	596	25	79	11.6	Prostate cancer mortality (74), overall survival (350)
This study	Population	Primary prostate cancer	3208	6[g]	100	14.3	Metastasis or death from prostate cancer (382)

[a]Abbreviations: NR, not reported; PSA, prostate-specific antigen.
[b]Patients in the study overall. Slightly smaller participant counts for certain polymorphisms in some studies (see Figure 1).
[c]Self-reported White race or European ancestry.
[d]Median, in years.
[e]Estimate for PSA progression; 6.5 years for overall mortality.
[f]The abstract identified on systematic review was by Kohli et al. (34). For methods and cohort description, see Zhang et al. (26). Results for *SLCO1B3* and *SLCO2B1* were kindly provided by the authors.
[g]Androgen deprivation therapy as primary therapy.

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Conflict of Interest Statement

K.L.P. and L.A.M. received research grants/funding from Janssen. G.C. has served as a scientific consultant for GuidePoint and received consultation fees. S.C.M. reports employment and stock ownership with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc. L.A.M. received grants/funding from AstraZeneca, has consulted for Bayer Pharmaceuticals, and is on the scientific advisory board for and has equity in Convergent Therapeutics. L.A.M. and K.H.S. received research funding, to Harvard University, from Veracyte. P.W.K. has investment interest in Convergent Therapeutics, Context Therapeutics LLC, and ESSA Pharma. He is a company board member for Convergent Therapeutics, Context Therapeutics, and Essa Pharma. He is a consultant/scientific advisory board member for ImmunisAI and PrognomIQ.

Data Availability

Procedures to access the cohort data were described previously (33). Data underlying the meta-analysis are available in the supplement.

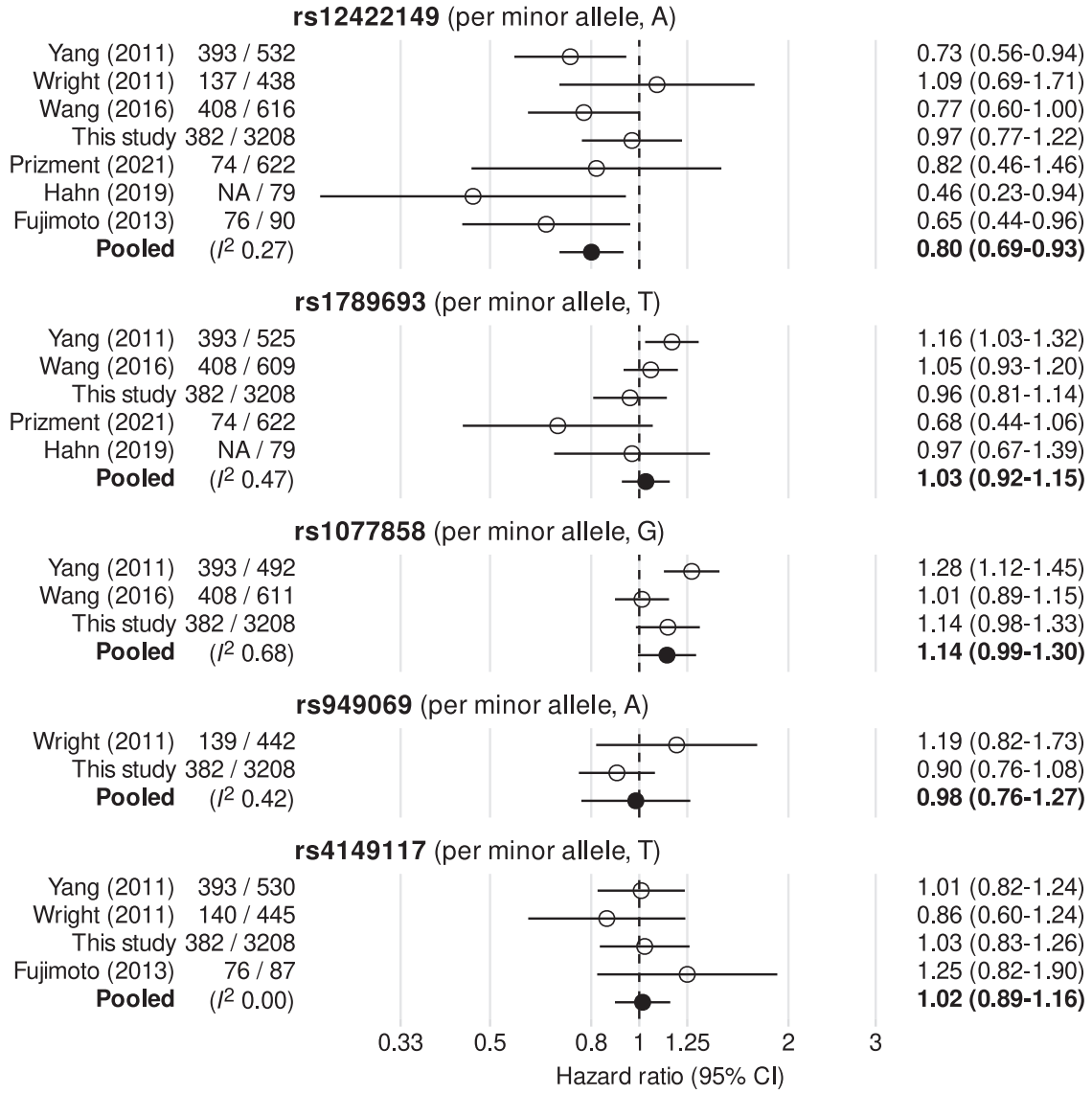

Figure 1. Meta-analysis for prostate cancer outcomes (clinical or biochemical progression, metastases, or death from prostate cancer). On the left-hand side, study name (year) and total event counts/total participants are shown. On the right-hand side, hazard ratio and 95% confidence interval are shown. NA, not available.

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