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Our study identified multiple novel loci associated with bladder cancer susceptibility, bringing the number of independent markers at genome-wide significance to 24. Genetic susceptibility markers, coupled with lifestyle risk factors such as smoking, could guide future preventive measures and screening strategies for bladder cancer.

Genome-wide Association Study of Bladder Cancer Reveals New Biological and Translational Insights

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Abstract

Background: Genomic regions identified via genome-wide association studies (GWAS) for bladder cancer risk provide new insights into etiology.

Objective: To identify new susceptibility variants for bladder cancer in a meta-analysis of new and existing genome-wide genotype data.

Design, setting, and participants: Data from 32 studies that includes 13 790 bladder cancer cases and 343 502 controls of European ancestry were used for meta-analysis.

Outcome measurements and statistical analyses: Log-additive associations of genetic variants were assessed using logistic regression models. A fixed-effects model was used for meta-analysis of the results. Stratified analyses were conducted to evaluate effect modification by sex and smoking status. A polygenic risk score (PRS) was generated on the basis of known and novel susceptibility variants and tested for interaction with smoking.

Results and limitations: Multiple novel loci associated with bladder cancer susceptibility (6p.22.3, 7q36.3, 8q21.13, 9p21.3, 10q22.1, 19q13.33) and improved signals from three known regions (4p16.3, 5p15.33, 11p15.5) were identified, bringing the number of independent markers at genome-wide significance ($p < 5 \times 10^{-8}$) to 24. The 4p16.3 *(FGFR3/TACC3)* locus was associated with a stronger risk for women than for men ($p = 0.002$). Bladder cancer risk was increased by interactions between smoking status and genetic variants at 8p22 (*NAT2*; multiplicative p value for interaction [$p_{M\text{-}I}$] = 0.004), 8q21.13 (*PAG1*; $p_{M\text{-}I} = 0.01$), and 9p21.3 (*LOC107987026/MTAP/CDKN2A*; $p_{M\text{-}I} = 0.02$). The PRS based on the 24 independent GWAS markers (odds ratio per standard deviation increase 1.49, 95% confidence interval 1.44–1.53), which also showed comparable results in two prospective cohorts (UK Biobank, PLCO trial), revealed an approximately fourfold difference in the lifetime risk of bladder cancer according to the PRS (eg, 1st vs 10th decile) for both smokers and nonsmokers.

Conclusions: We report novel loci associated with the risk of bladder cancer that provide clues to its biological underpinnings. Using 24 independent markers, we constructed a PRS to stratify lifetime risk. The PRS combined with smoking history and other established risk factors for bladder cancer risk has the potential to inform future screening efforts for bladder cancer.

Patient summary: We identified new genetic markers that provide biological insights into the genetic causes of bladder cancer. These genetic risk factors combined with lifestyle risk factors, such as smoking, may inform future preventive and screening strategies for bladder cancer.

Keywords

Bladder cancer; Germline genetics; Genome-wise association study; Gene-environment interaction

1. Introduction

Previous genome-wide association studies (GWAS) have identified more than a dozen loci associated with bladder cancer risk among individuals of European [1-10] and East Asian [11-14] ancestry. Follow-up studies of GWAS regions [9,15-20] have yielded important insights into underlying molecular mechanisms. It is estimated that these susceptibility loci explain approximately 12% of the familial risk of bladder cancer [1], suggesting that more loci are yet to be identified [21].

Cigarette smoking is the leading risk factor for bladder cancer, and interactions with genetic susceptibility variants have been identified [7,22]. The combined effects of smoking and genetic risk factors, as well as other risk factors such as occupational exposures [23], may have important clinical implications for risk stratification and efforts to achieve early cancer detection.

We conducted a meta-analysis of genome-wide genotype data across 32 international studies. By doubling the number of previously published cases with genome-wide scan data to include 13 790 bladder cancer cases and 343 502 control subjects of European ancestry, we aimed to identify novel susceptibility loci and evaluate interactions with smoking.

2. Materials and methods

2.1. Study sample

We analyzed data from published and unpublished genotyped studies (Supplementary Table 1). Cases were defined as histologically confirmed primary carcinoma of the urinary bladder of all stages, including carcinoma in situ (International Classification of Diseases for Oncology, C670-C679, 188); cases in the UK Biobank include only those with tumor stage ≥T1 [24]. All histological subtypes were included. Each study obtained informed consent from participants and approval from the relevant institutional review board.

2.2. Statistical analyses

The samples were analyzed separately for nine study/array groups using individual genotypes from seven genotyping platforms (Supplementary Table 1). Imputation was performed with the Michigan Imputation Server, using the Haplotype Reference Consortium dataset (HRC release 1.1). Two studies (CNIO/UROMOL and deCODE) provided summary-level results after imputation (Supplementary material). Individuals of European ancestry were identified using principal component analysis. After quality control, data for 13 447 cases and 342 580 control subjects of European ancestry were analyzed, with a genomic inflation statistic for the meta-analysis of $\lambda = 1.098$.

Log-additive effects for 9 680 336 genotyped/imputed variants were calculated using SNPTEST, adjusted for array-specific significant principal components, separately for each study/array group and meta-analyzed using a fixed-effects model to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Tests of heterogeneity were performed using Cochrane's Q statistic. Stratified analyses were conducted to evaluate effect modification by sex and smoking status (never vs ever, and never vs former vs current smokers). Polytomous

logistic regression was used for analyses of low-grade or high-grade non–muscle-invasive bladder cancer (NMIBC) or muscle-invasive bladder cancer (MIBC); only subjects with complete stage/grade information were used for these analyses. Summary statistics were used for: (1) a linkage disequilibrium (LD) score regression analysis (Supplementary Fig. 1), and (2) GWAS analysis of regulatory or functional data with LD correction (GARFIELD; Supplementary Fig. 2).

For calculation of the polygenic risk score (PRS), the GWAS discovery set included tumors of all stages; independent PRS validation data sets are described in the Supplementary material. The proportion of the familial relative risk explained was calculated [25] using an overall familial relative risk of 1.8 for bladder cancer (reported in [26]). Additive and multiplicative tests for interactions between individual markers and the 24-marker PRS with smoking status were computed using the R package CGEN (R Foundation for Statistical Computing, Vienna, Austria). To identify a subgroup of high-risk individuals who could potentially be targeted for greater preventive efforts and surveillance, we used the Individualized Coherent Absolute Risk Estimator (iCARE) software (iCare Software, Boxborough, MA, USA) to estimate the residual lifetime absolute risk (AR) of bladder cancer by PRS deciles for 50-yr-old White non-Hispanic never, former, and current smokers for males and females separately over a projected 30-yr span (Supplementary material).

2.3. In silico functional analyses of new susceptibility loci

Expression quantitative trait loci (eQTL) analysis of all new loci was performed using data from The Cancer Genome Atlas (TCGA, 412 MIBC cases) and UROMOL (359 NMIBC cases). Colocalization analysis of GWAS and eQTL signals was performed with R packages LocusCompareR (R Foundation for Statistical Computing) and *coloc* (Supplementary material).

A transcriptome-wide association study (TWAS) for bladder cancer risk was conducted using 412 TCGA bladder tumors and normal tissues from GTEx (48 tissue types, 80–491 samples per tissue; Supplementary material).

Formalin-fixed, paraffin-embedded tumor tissue blocks from the New England Bladder Cancer Study (NEBCS), the Spanish Bladder Cancer EPICURO Study (SBCS), and the UROMOL consortium were used to determine *FGFR3* somatic mutations (Supplementary material).

3. Results

3.1. Identification of GWAS signals

Using genome-wide data from nearly 7000 new cases combined with previous GWAS, seven new genome-wide significant loci were identified. Five loci are novel: 6p22.3 (rs72826305, *CASC15/LOC105374970*; $p = 1.81 \times 10^{-10}$), 7q36.3 (rs2125484, *LOC389602*; $p = 1.42 \times 10^{-9}$), 9q31.1 (rs4743687, *SMC2*; $p = 2.05 \times 10^{-8}$), 10q22.1 (rs7076867, *COL13A1*; $p = 5.60 \times 10^{-13}$), and 19q13.33 (rs411482, *SULT2B1-FAM83E*; $p = 1.16 \times 10^{-12}$; Table 1, Supplementary Table 2). Two signals [1,2] that had previously approached but had not yet

achieved genome-wide significance were confirmed for 6p22.3 (rs6910215, *CDKAL1*; $p = 1.05 \times 10^{-8}$) and 8q21.13 (rs5003154, *PAG1*; $p = 1.15 \times 10^{-10}$).

Genome-wide significant associations for all published regions were confirmed (Supplementary Table 3), except for rs10936599 (3q26.2 *MYNN/TERC*; $p = 1.16 \times 10^{-6}$) [2]. Based on conditional analyses, two previous GWAS signals were improved by correlated markers: rs2896518 at 4p16.3 (*FGFR3/TACC3*; $p = 5.28 \times 10^{-15}$) and rs2242652 or rs10069690 at 5p15.33 (*CLPTM1L/TERT*; $p = 4.06 \times 10^{-15}$ and $p = 1.54 \times 10^{-14}$, respectively). At 11p15.5, a second independent signal was identified, rs7937265 ($p = 1.10 \times 10^{-8}$). Within the 1p13.3 locus, which harbors the *GSTM1* deletion, a well-established genetic risk factor for bladder cancer [7,27], we explored a strong association signal for a low-quality imputed marker, rs36209093 ($p = 3.21 \times 10^{-18}$; Supplementary Table 4, Supplementary Fig. 3). A proxy marker (chr1:110229772) effectively tagged the *GSTM1* deletion, improving the association signal ($p = 8.84 \times 10^{-23}$).

3.2. Genome-wide analyses stratified by smoking status and sex

Results for stratified analyses by study/array groups are presented in Supplementary Table 5. Among current and ever smokers (ie, current and former smokers combined), rs1414253 at 9p21.3 achieved genome-wide significance ($p = 9.37 \times 10^{-9}$ for current smokers and $p = 1.23 \times 10^{-8}$ for ever smokers; Table 1). This effect is driven primarily by current smokers (Supplementary Table 6). Analyses stratified by sex did not reveal new signals, but effect modification was observed for rs2896518 at 4p16.3 (*TACC3/FGFR3*, interaction $p = 0.002$); the effect was larger for women (OR 1.34, 95% CI 1.22–1.47; $p = 1.93 \times 10^{-9}$) than for men (OR 1.12, 95% CI 1.06–1.18; $p = 4.20 \times 10^{-5}$; Supplementary Table 7). Results were unchanged after adjustment for smoking. The sex-specific effect for rs2896518 was pursued with respect to somatic *FGFR3* mutations in a set of predominantly NMIBC tumors (NEBCS, SBCS, and UROMOL). Somatic *FGFR3* mutations were more common among females than among males (OR 1.33, 95% CI 1.07–1.66 for females vs males; Table 2, Supplementary Table 8). Furthermore, each additional rs2896518-A risk allele was associated with an increase in the frequency of *FGFR3* mutations (OR 1.19, 95% CI 1.01–1.40; Table 2; Supplementary Table 8 provides additional results for TCGA). Analyses of $FGFR3^{+}$ mutation status in TCGA (MIBC only) did not show a consistent association with female sex on multivariate analysis; however, a positive association per rs2896518-A risk allele was observed (OR 1.84, 95% CI 1.15–2.92; Supplementary Table 8).

3.3. NMIBC- and MIBC-stratified GWAS analyses

Heterogeneity of risk by muscle invasiveness was observed for two loci, rs2896518 (*TACC3/FGFR3*; p for heterogeneity [p_H] $= 2.67 \times 10^{-9}$) and rs7937265 (*TNNT3/LSP1*; $p_H = 0.027$; Supplementary Table 9). For both markers, the associations were strongest for low-grade NMIBC ($p_H = 1.30 \times 10^{-11}$ and $p_H = 3.27 \times 10^{-4}$, respectively). In addition, rs5003154 (*PAG1*) showed significant heterogeneity among NMIBC subtypes ($p_H = 0.01$) with a stronger association observed for low-grade NMIBC. Analysis of the novel signals in TCGA did not reveal associations with consensus molecular classification subtypes [28], while the *PAG1*-rs5003154-C risk allele was enriched in iLuminal compared to iBasal tumors

[29] (Supplementary Table 10). In both NMIBC and MIBC mRNA subtypes, higher *PAG1* expression was detected in luminal tumors (Supplementary Fig. 4).

3.4. In silico functional analyses

In silico analysis (GARFIELD) showed that risk variants were significantly enriched for putative regulatory characteristics (Supplementary Fig. 2). Analyses of TCGA and UROMOL data revealed only one eQTL in the same direction in both sets (rs5003154-C risk allele and *PAG1* expression: $\beta = -0.142$, $p = 0.035$ for TCGA, and $\beta = -0.195$, $p = 3.7 \times 10^{-15}$ for UROMOL; Supplementary Table 11). The posterior probability for colocalization of the GWAS signal and eQTL for *PAG1* expression was 98.9% for UROMOL (NMIBC) and was weak (19.6%) for TCGA (MIBC; Supplementary Fig. 5). TWAS results for TCGA data indicated that a higher risk of bladder cancer was associated with genetically predicted expression of some genes identified in previous bladder cancer analyses [18,27]. The predicted gene expression of *FUT2* (uncorrected $p = 5.84 \times 10^{-8}$) near the novel GWAS marker rs411482 (19q13.33) remained significant after correction for multiple testing (Supplementary Table 12 for bladder tissue and data sets for normal tissues).

3.5. Gene-smoking interactions

A previous multiplicative interaction between smoking and the 8q22 locus (*NAT2*) [27,30] was confirmed, indicating higher risk among ever smokers with the *NAT2* slow acetylation genotype/phenotype (interaction $p = 0.004$). Two other loci also showed evidence of multiplicative interaction with ever smoking, namely 9p21.3 (*CDKN2A*; rs1414253, interaction $p = 0.02$; Supplementary Table 13) and 8q21.1 (*PAG1*; rs5003154; interaction $p = 0.01$; Supplementary Table 13). For rs1414253 (9p21.3), the higher risk was for smokers, while for rs5003154 (8q21.1) the higher risk was observed for never smokers.

3.6. PRS

Using the combined set of 24 independent GWAS markers, a PRS was generated (Supplementary Table 14). In our discovery GWAS set, the OR per standard deviation increase in the PRS was 1.49 (95% CI 1.44–1.53) after adjustment for age, sex, and study/array groups. This 24-marker PRS association was externally evaluated using data from two independent series of cases and controls from the PLCO cancer screening trial and the UK Biobank (Supplementary material) and was found to be strongly associated with risk, with hazard ratios of 1.51 (95% CI 1.38–1.65) and 1.32 (95% CI 1.21–1.44), respectively (Supplementary Table 15). Overall, we estimate that the 24-marker PRS explains 14.8% of the familial risk of bladder cancer for individuals of European ancestry. In preliminary analyses using our GWAS discovery set, there was evidence of additive (Supplementary Table 16), but not multiplicative, interaction between smoking and the PRS. Notably, differences in the AR of bladder cancer due to smoking between the low and high PRS deciles indicate that the potential impact of smoking cessation is greater for those at higher genetic risk than for individuals at lower genetic risk (additive p for interaction = 0.01 for ≥80th vs ≥10^{th} PRS decile comparing current vs former smokers).

Further exploratory analyses in our discovery set evaluated how the PRS could estimate the residual lifetime AR of bladder cancer in the US population on the basis of incidence,

mortality, and cigarette smoking data for 50-yr-old White non-Hispanic men and women over the next 30 yr, overall, by PRS decile categories, and for the highest percentiles (1% or 5%; Fig. 1A,B). For males, the overall average lifetime AR was 1.9% for never smokers (range 0.9–3.5% by PRS deciles), 4.0% for former smokers (range 1.9–7.4% by PRS deciles), and 7.1% for current smokers (range 3.4–13.0% by PRS deciles). For females, the overall average lifetime AR was 0.4% for never smokers (range 0.2–0.8% by PRS deciles), 1.1% for former smokers (range 0.5–2.0% by PRS deciles), and 2.0% for current smokers (range 0.9–3.7% by PRS deciles). For the highest 1% PRS percentile, the average lifetime AR for males differed substantially by smoking status, with risks of 5.0%, 10.3%, and 18.0% for never, former, and current smokers, respectively. For the highest 1% PRS percentile, the corresponding lifetime AR for females was 1.2%, 2.9%, and 5.3% for never, former, and current smokers, respectively. Notably, stratification by this PRS identified a subgroup of never-smoker males and females who had a higher genetic risk of developing bladder cancer in comparison to current smokers with low genetic risk (Fig. 1C). Using census estimates and the above inputs, we estimated the number of cancers that could be prevented according to the combination of PRS and smoking status (Fig. 2). For example, among 50-yr-old non-Hispanic White individuals in 2017 (~2.6 million people, Fig. 2A) we estimated that a successful smoking cessation program for current smokers at the highest genetic risk (ie, 10th PRS decile) would prevent 2061 cases (1611 males, 450 females; Fig. 2B).

4. Discussion

We report a new meta-analysis of bladder cancer using genome-wide data for nearly 7000 new cases combined with previous GWAS in which the number of susceptibility loci has nearly doubled.

Genome-wide in silico functional analyses identified enrichment of associated variants within regulatory regions. For one of the GWAS regions, at 8q21.13, we observed strong colocalization of the GWAS and eQTL signals for *PAG1* expression, especially in NMIBC, suggesting a shared functional effect of the lead marker, rs5003154, on *PAG1* expression, bladder cancer risk, and a previously undescribed role in the luminal differentiation program. Our TWAS results implicate *FUT2* as a candidate gene for the 19q13.33 locus (rs411482); this region is also associated with risks of cancer of the colon, pancreas, endometrium, cervix, and lung [31-33] and differential susceptibility to infections [34]. Evidence of pleiotropy was also noted for other new GWAS loci. Specifically, rs4743687 (9q31.1, *SMC2*) is linked to variants associated with pancreatic cancer [35], breast cancer [25], basal cell carcinoma [36], and ovarian cancer [37]. The single-nucleotide polymorphism rs7937265 (11p15.5, *TNNT3-LSP1*) is linked to variants associated with monocyte count, systolic blood pressure, cardiovascular disease, and breast cancer risk [38].

Select loci overlap with regions in which somatic alterations are frequently observed in bladder tumors. Specifically, rs6910215 (6p22, near *E2F3*) is located within a region frequently amplified or overexpressed in bladder tumors, impacting cell cycle regulation [39]. Similarly, the novel variants within 9p21 (*CDKN2A*) are in a region frequently deleted in bladder tumors [40], and our results suggest an interaction with smoking.

In our meta-analysis, the effect of rs2896518 (*TACC3/FGFR3*, 4p16.3) was stronger for women (interaction $p = 0.002$) and did not change on adjustment for smoking. *FGFR3* somatic mutations are a hallmark of NMIBC, detectable in up to 80% of Ta tumors [40]. It is notable that an excess of *FGFR3* somatic mutations was observed among women, despite lower bladder-cancer incidence rates in comparison to men [41]. The associations with somatic *FGFR3* mutations were stronger for the new 4p16.3 lead marker rs2896518 (Table 2) than for the previous lead, rs798766 [10,23]. Further detailed exploration of sex differences and differential patterns by stage between germline variants and somatic mutations at this locus are warranted, including evaluation of differences by expression subtypes, as these too may show differences by sex [42] and stage. More complete data on stage, grade, sex, and smoking status will be needed in subsequent studies to explore our preliminary findings. We observed an interaction between the newly generated 24-marker PRS and cigarette smoking on the additive scale, suggesting important lifetime risk differences. Projections for the average lifetime AR of bladder cancer for never, former, and current smokers among males and females revealed an approximately fourfold difference, depending on the PRS decile (Fig. 1A,B). Furthermore, the lifetime AR distribution by smoking status overlapped at the upper tail of the never-smoker and lower tail of the current-smoker distributions, identifying a subgroup of never-smoker males and females with comparable or even higher genetic risk of developing bladder cancer in comparison to current smokers with low genetic risk (Fig. 1C).

The 24-marker PRS generated on the basis of this meta-analysis was also evaluated in two prospective cohorts and showed comparable results. Extension of the GWAS to a larger set should identify additional susceptibility loci and generate a more precise PRS [43]. The development of a risk model that includes the PRS and lifestyle/environmental risk factors will require further characterization of the relative risk associated with these factors and exploration of their interactions. Furthermore, the absolute risk projections need prospective validation [43,44]. Since our PRS was constructed using data for individuals of European ancestry, the AR estimates may not be accurate when applied to individuals of other ancestries, for whom genetic studies are limited. In this regard, a future goal should be to conduct larger, diverse GWAS that will allow cross-ancestry studies, which have been successful for other cancers such as prostate cancer. The utility of well-calibrated risk models will still depend on advances in clinical screening tools for those at high risk of bladder cancer.

Although smoking cessation is the most powerful way to prevent bladder cancer, these efforts might be further improved by identification of individuals with elevated genetic risk because of both common and rare high-penetrance variants (including familial bladder cancer) who may especially benefit from smoking cessation or be directed to more intense clinical management under high-risk scenarios (eg, recurrent hematuria or urinary tract infections). A limitation of the study is that we could not test associations with disease progression or treatment response, as these clinical data were not available. These issues warrant future study.

5. Conclusions

We identified multiple susceptibility variants associated with bladder cancer risk. Prospective validation of a risk prediction model that includes the PRS, smoking status, and lifestyle/environmental factors represents the next step towards developing effective instruments for precision prevention oncology for bladder cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing statement:

Summary statistics for all the analyses presented here will be available on dbGaP under accession number TBD (currently being generated).

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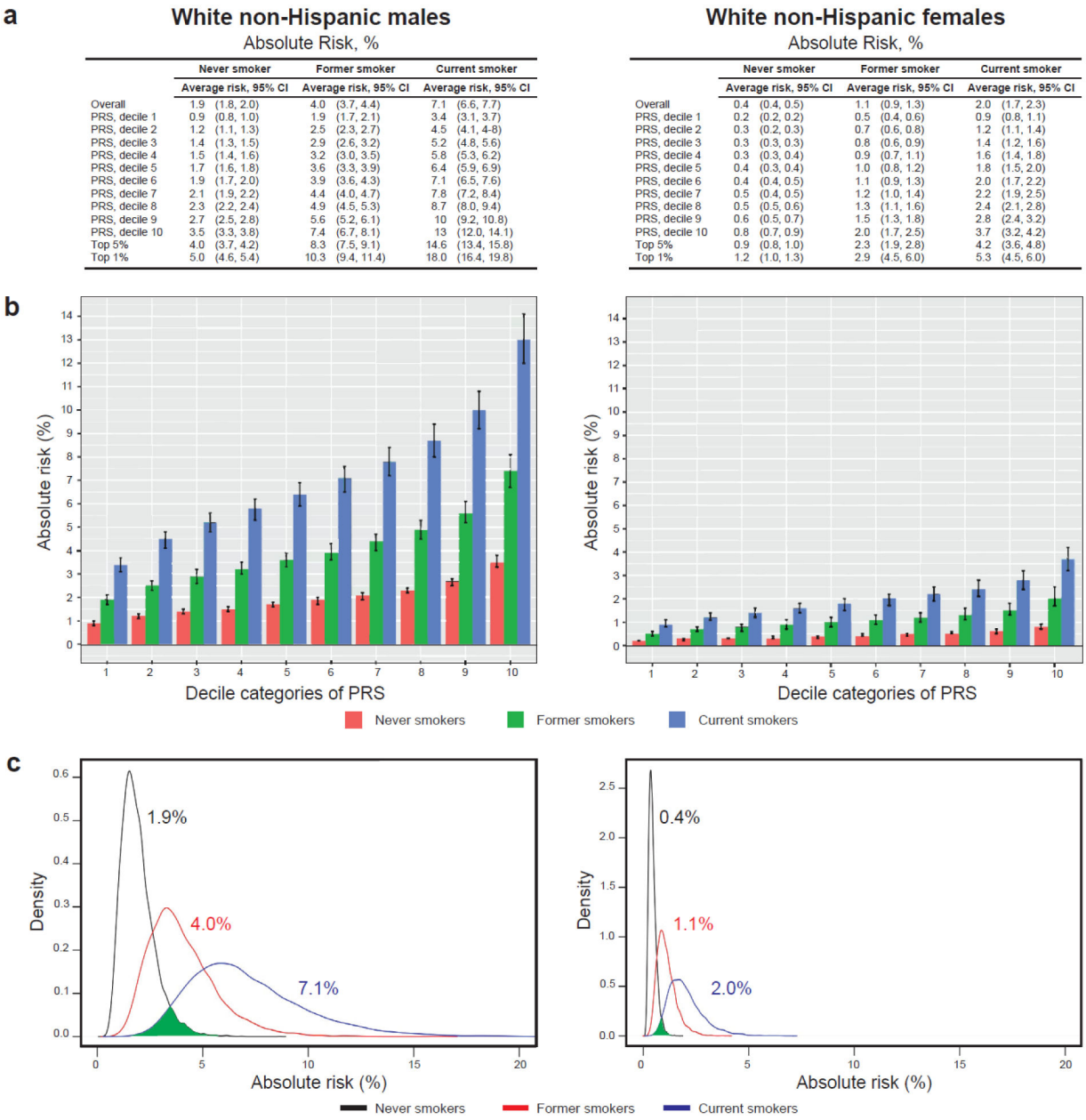


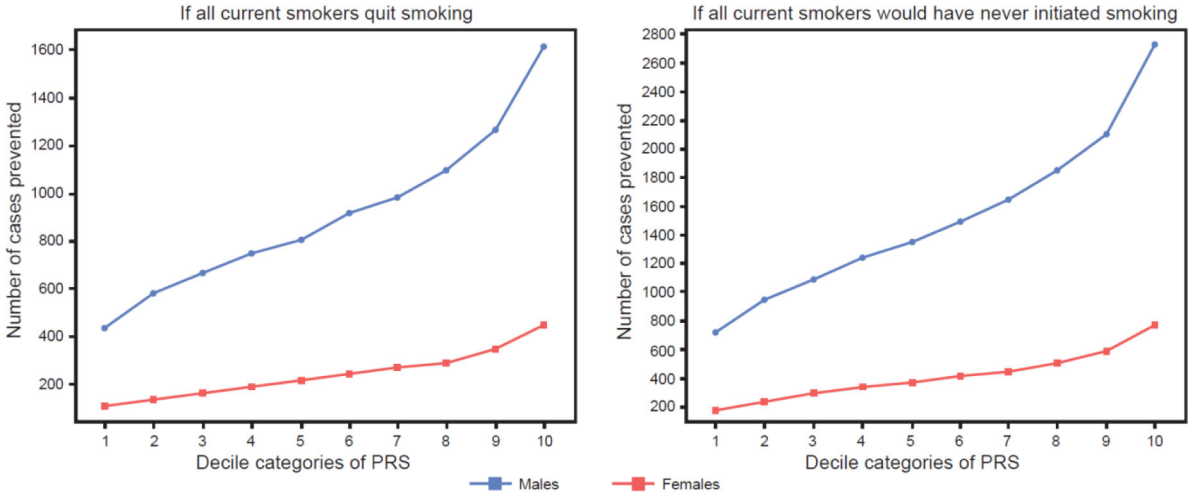
Figure 1.

Estimates of absolute risk of bladder cancer for White non-Hispanic males and females by polygenic risk score (PRS) and smoking status. (A) Average and top (5% and 1%) absolute risks and 95% confidence intervals (CIs) for never, former, and current smokers by PRS deciles for White non-Hispanic males and females (age 50–80 yr). (b) Bar graph of average absolute risk for never, former, and current smokers showing that the risk difference increases with PRS decile. (C) Population density plots of the entire absolute risk distributions for male and female never, former, and current smokers. Green shading depicts the overlap in absolute risk distribution for never and current smokers, indicating that some proportion of never smokers at high genetic risk have the same absolute risk of bladder cancer as current smokers at low genetic risk.

a

Population of 50-year old	Males	Females
Resident population (Census Estimate, July 1, 2017), n	1,990,382	2,045,713
Non-Hispanic Whites (National Health Interview Survey 2015-2017), %	65.7	62.4
Resident population: non-Hispanic Whites, n	1,307,681	1,276,525
Never smokers, n (%) Average risk, % Number of cases	623,764 (47.7) 1.9 11,852	741,661 (58.3) 0.4 2,967
Former smokers, n (%) Average risk, % Number of cases	396,227 (30.3) 4.0 15,849	270,623 (21.2) 1.1 2,977
Current smokers, n (%) Average risk, % Number of cases	287,690 (22.0) 7.1 20,426	264,241 (20.7) 2.0 5,285

b



c

Decile	1	2	3	4	5	6	7	8	9	10
Males	431	576	662	748	805	921	978	1093	1266	1611
Females	106	132	159	185	212	237	264	290	344	450

Decile	1	2	3	4	5	6	7	8	9	10
Males	719	950	1093	1237	1352	1496	1640	1841	2100	2733
Females	185	238	291	344	370	422	449	502	581	767

Figure 2.

Estimates of the number of bladder cancer cases that could be prevented according to the combination of polygenic risk score (PRS) and smoking status. (A) Inputs and data sources used in the analyses. (B) The number of bladder cancer cases that could be prevented by PRS deciles for males and females under two scenarios: (1) if all current smokers quit smoking and (2) if all current smokers had never started smoking. (C) Estimates of the number of cases that could be prevented for males and females by PRS deciles for the scenarios in B.

Table 1 –

Novel loci associated with bladder cancer susceptibility [a]

SNP	Band	Position (hg19)	Gene region	Allele		EA frequency		Studies (*n*)	Cases (*n*)	CTR (*n*)	OR (95% CI)	*p* value	Q [b]
				EA	Ref	CTR	Cases						
Previously identified regions													
rs2896518	4p16.3	1757559	*TACC3, FGFR3*	A	G	0.21	0.23	9	13447	342 580	1.17 (1.13–1.22)	5.28×10^{-15}	0.1901
rs2242652	5p15.33	1280028	*CLPTM1L, TERT*	G	A	0.80	0.82	9	13447	342 580	1.18 (1.14–1.24)	4.06×10^{-15}	0.9181
rs10069690		1279790		C	T	0.74	0.76	9	13447	342 580	1.16 (1.12–1.22)	1.54×10^{-14}	0.7989
rs7937265	11p15.5	1947800	*TNNT3, LSP1*	G	C	0.19	0.21	9	13447	342 580	1.13 (1.08–1.18)	1.10×10^{-8}	0.1406
Newly identified regions													
rs6910215	6p22.3	20783394	*CDKAL1*	C	T	0.57	0.59	9	13447	342 580	1.10 (1.06–1.14)	1.05×10^{-8}	0.6166
rs72826305	6p22.3	21826729	*CASC15/ LOC105374970*	C	T	0.34	0.37	9	13447	342 580	1.12 (1.08–1.16)	1.81×10^{-10}	0.4132
rs2125484	7q36.3	155759638	*LOC389602*	G	A	0.58	0.60	9	13447	342 580	1.11 (1.07–1.15)	1.42×10^{-9}	0.7918
rs5003154	8q21.13	81986953	*PAG1*	C	T	0.51	0.54	9	13447	342 580	1.11 (1.08–1.15)	1.15×10^{-10}	0.8466
rs4743687	9q31.1	106856910	*SMC2*	C	T	0.44	0.46	9	13447	342 580	1.10 (1.06–1.13)	2.05×10^{-8}	0.0659
rs7076867	10q22.1	71582996	*COL13A1*	C	T	0.95	0.96	9	13447	342 580	1.31 (1.22–1.41)	5.60×10^{-13}	0.886
rs411482	19q13.33	49103447	*SULT2B1-FAM83E*	C	T	0.61	0.63	9	13447	342 580	1.13 (1.09–1.17)	1.16×10^{-12}	0.3869
In smokers													
rs1414253	9p21.3	21755630	**LOC107987026, MTAP/ CDKN2A**	A	G	0.42	0.43						
Ever smokers								8	9251	57124	1.14 (1.09–1.19)	1.23×10^{-8}	0.5183
Current smokers [c]								6	3286	2802	1.27 (1.17–1.38)	9.37×10^{-9}	0.1519

SNP = single-nucleotide polymorphism; EA = effect allele; Ref = reference; CTR = control; OR = odds ratio; CI = confidence interval

[a] A fixed-effects meta-analysis by study was used to calculate the combined OR, 95% CI, and *p* trend for the EA, adjusted for age and array-specific principal components.

[b] Cochran's Q (measure of heterogeneity) *p* value.

[c] rs10811586, which is in linkage disequilibrium with rs1414253 (D' = 0.87, R^2 = 0.72 in Europeans in 1000 Genomes), showed a slightly more significant association among current smokers (p = 2.29E-09).

Table 2 –

Case-case ORs for the associations of sex and rs2896518 mutation with *FGFR3* somatic mutations [a]

Study	Female versus male			rs2896518-A risk allele		
	Cases (*n*)		OR (95% CI) [b]	Cases (*n*)		OR (95% CI) [b]
	FGFR3 wt	*FGFR3* M^+		*FGFR3* wt	*FGFR3* M^+	
SBCS	551	391	1.18 (0.80–1.73)	480	338	1.07 (0.84–1.37)
NEBCS	171	174	1.59 (0.96–2.64)	132	142	1.46 (0.96–2.21)
UROMOL	401	460	1.35 (0.98–1.87)	291	373	1.23 (0.95–1.59)
Meta-analysis	1123	1025	1.33 (1.07–1.66)	885	816	1.19 (1.01–1.40)
***p* value**			0.011			0.039

OR = odds ratio; CI = confidence interval; wt = wild type; M^+ = mutation; SBCS = Spanish Bladder Cancer EPICURO study; NEBCS = New England Bladder Cancer Study.

[a] Details on *FGFR3* mutation analyses are provided in the Supplemental material.

[b] Unadjusted OR for the odds of having an *FGFR3* mutation; additionally adjusted ORs are provided in Supplementary Table 8.