Replication and Genetic Risk Score Analysis for Pancreatic Cancer in a Diverse Multiethnic Population

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ABSTRACT

Background: Genome-wide association studies (GWAS) have identified several SNPs associated with pancreatic cancer. No studies yet have attempted to replicate these SNPs in US minority populations. We aimed to replicate the associations of 31 GWAS-identified SNPs with pancreatic cancer and build and test a polygenic risk score (PRS) for pancreatic cancer in an ethnically diverse population.

Methods: We evaluated 31 risk variants in the Multiethnic Cohort and the Southern Community Cohort Study. We included 691 pancreatic ductal adenocarcinoma (PDAC) cases and 13,778 controls from African-American, Japanese-American, Latino, Native Hawaiian, and white participants. We tested the association between each SNP and PDAC, established a PRS using the 31 SNPs, and tested the association between the score and PDAC risk.

Results: Eleven of the 31 SNPs were replicated in the multiethnic sample. The PRS was associated with PDAC risk [OR top vs. middle quintile = 2.25 (95% confidence interval, 1.73–2.92)]. Notably, the PRS was associated with PDAC risk in all ethnic groups except Native Hawaiian (OR per risk allele ranged from 1.33 in Native Hawaiians to 1.91 in African Americans; P heterogeneity = 0.12).

Conclusions: This is the first study to replicate 11 of the 31 GWAS-identified risk variants for pancreatic cancer in multiethnic populations, including African Americans, Japanese Americans, and Latinos. Our results also suggest a potential utility of PRS with GWAS-identified risk variants for the identification of individuals at increased risk for PDAC across multiple ethnic groups.

Impact: PRS can potentially be used to stratify pancreatic cancer risk across multiple ethnic groups.

Introduction

Pancreatic cancer is the fourth leading cause of cancer deaths in the United States with over 56,000 new cases and 45,000 deaths in 2019 (1). By 2030, pancreatic cancer is projected to be the second leading cause of cancer-related death (2). Diagnosis at a late stage is common due to lack of symptoms at early stage of disease and regular forms of screening (3). These characteristics result in a 5-year survival of only 9% (1), emphasizing the importance of primary prevention strategies for this disease.

Pancreatic cancer incidence differs by ethnicity. African Americans experience 1.36 times the rate of pancreatic cancer (10.4 per 100,000) relative to non-Hispanic whites (7.7; ref. 4). Differences in incidence rates are observed across other ethnic groups [Hispanic (7.1), Japanese (8.1), Asian/Pacific Islander (6.2 per 100,000)]. In the Multiethnic Cohort (MEC), the incidence rates of pancreatic cancer are notably higher among Native Hawaiians (1.8 times that of whites), followed by African Americans and Japanese Americans (1.3–1.4 times that of whites; ref. 5). Epidemiologic studies have associated body mass index (BMI; refs. 5–7), type 2 diabetes (5, 8, 9), diet patterns (10, 11), and smoking (5, 12) with pancreatic cancer. In the MEC, approximately 20% of pancreatic cancer can be attributed to these factors (5).

Common genetic variants have been associated with pancreatic cancer risk in genome-wide association studies (GWAS; refs. 13–21). So far, these GWAS have identified 31 risk variants for pancreatic cancer. Twenty-two were identified by the PanScan and the PanC4 studies, composed of populations of primarily European ancestry (13–15, 18, 19, 21). Of the remaining variants, four were discovered in Japanese and five in Chinese (16, 17, 20).

The associations between GWAS variants and pancreatic cancer have yet to be examined in other ethnic groups, especially in high-risk African Americans and other minority populations. Few SNPs identified in European ancestry replicated in Asian samples. In Chinese, Wang and colleagues replicated 4 SNPs identified in GWAS and pathway analysis in Europeans, Chinese, and Japanese (22). Among Japanese, Nakatochi and colleagues have replicated 13 GWAS-significant and suggestive loci, discovered in Europeans, Japanese, and Chinese (23); Ueno and colleagues have replicated one European ancestry loci in Japanese (24). Similarly, there are limited cross-ethnic replications among Europeans (15, 25), with only one Japanese-identified SNP replicated in Europeans (15). In addition, three other Asian GWAS have also reported on replication of GWAS-identified SNPs in their samples (16, 17, 20). Lack of replication of pancreatic cancer–associated SNPs across ethnic groups may be due to low minor allele frequencies, monomorphic loci, and differences of linkage disequilibrium of tagging SNPs between ethnic groups. Identifying the association of these

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SNPs with pancreatic cancer in a multiethnic population, and in ethnic-specific analyses, will help us identify the value of these SNPs for disease prediction in an admixed sample.

In this study, we assessed the transportability of prior GWAS findings in an ethnically diverse population and examined how these variants contribute to pancreatic cancer risk across populations. We first attempted to replicate the 31 GWAS-significant risk variants in the MEC and the Southern Community Cohort Study (SCCS). Using the 31 SNPs, we then built a multiethnic polygenic risk score (PRS) and assessed its association with pancreatic cancer risk.

Materials and Methods

Study population

This study included case–control samples within the MEC and SCCS. Information on recruitment, characteristics, and case ascertainment in the MEC and SCCS has been described (refs. 26, 27; Supplementary Methods Text S1). Briefly, the MEC is a population-based prospective cohort study initiated between 1993 and 1996 to investigate cancer etiology. The MEC consists of over 215,000 men and women from Los Angeles County and Hawaii who were 45 to 75 years old at enrollment and from these racial/ethnic groups: African Americans, Japanese Americans, Latinos, Native Hawaiians, and whites. The SCCS was initiated in 2002 to investigate sources of racial disparities in cancer and chronic disease. The SCCS participants were mainly African Americans and whites between the ages of 40 and 79 who resided in one of 12 US southern states. At baseline, the MEC and SCCS gathered detailed information on demographics, lifestyle, diet, anthropometry, reproductive history, and medical history. In both cohorts, cancer cases were identified through annual linkage to state cancer registries. Pancreatic cancer cases were defined as primary invasive pancreatic cancer with pancreatic ductal adenocarcinoma (PDAC) histology (ICD-O-3 code C25). Controls were selected by matching to incident cases based on age, sex, and ethnicity. For the MEC, we also added eligible controls (without PDAC) with genotype data from prior GWAS. We conducted all analyses with the original cases and matched controls then with added controls. We present the results using the added controls because the effect estimates were similar between analyses, and we had improved statistical power.

Genotyping, quality control, and genotype imputation

Samples were genotyped using the Multi-Ethnic Genotyping Array chip (Illumina), which was developed to ensure genome-wide coverage of variants down to 1% frequency in non-European ancestry populations. Samples underwent an intensive quality control process including SNP call-rate filtering, sample call rate filtering, concordance checks of inter- and intraplate controls, removal of redundant or discordant variants based on location and call rates, and removal of SNPs with race-specific allele frequency differences over 25% in comparison with 1000G phase 3 race-specific estimates (Supplementary Fig. S1). Following QC, 932,530 SNPs, 691 cases, and 13,778 controls were used for imputation. The sample was stratified based on self-reported ethnicity, then imputed using Minimac3, ShapeIT v2, and the cosmopolitan 1000 Genomes Project reference panel (Phase 3 v5).

Statistical analysis

Participants with missing covariate values or with implausible values for age, sex, diabetes, and BMI (kg/m^2) were removed from analysis. Related samples (first- and second-degree relatives) were identified using KING software for robust relationship inference then removed based on a kinship coefficient of 0.0884 or greater (Supplementary Fig. S2; ref. 28).

SNP and PDAC associations were examined using logistic regression, adjusting for age at sample collection, sex, study, BMI, diabetes, and population stratification using principal components (PC 1–6). PCs were estimated using PLINK and a set of >50,000 independent SNPs (29). Most global ancestry variation among the five ethnic groups was captured in the first six PCs (Supplementary Fig. S3). Measures of association were reported on the ratio scale along with corresponding likelihood ratio test (LRT) P values. As a sensitivity analysis, we estimated multiethnic associations by meta-analyzing ethnic-specific results using both fixed-effect and random-effects models. We present multiethnic pooled results because there was no effect heterogeneity between the pooled multiethnic analysis and the meta-analyses. All SNPs were modeled as log odds of PDAC per risk allele (0, 1, or 2). A log odds weighted PRS was estimated for each participant by multiplying the multiethnic log odds for each of the 31 SNPs by the number of risk alleles at the given loci, then summing all values. This PRS took the following form: $PRS = \beta_1 x_1 + \beta_2 x_2 + \ldots \beta_k x_k + \beta_n x_n$. In this algorithm, β_1 is the log odds ratio for risk of PDAC associated with a per allele increase in risk for a given SNP in our replication analysis. x_k is the number of risk alleles an individual has for the corresponding SNP (0, 1, or 2). We additionally conducted sensitivity analyses using the following alternative weighting methods: external weights, external weights only using 22 SNPs from European studies, unweighted, ethnic-specific internal weights, and multiethnic weights from a meta-analysis of ethnic-specific associations from the replication, using both a random-effects and a fixed-effect.

Table 1. Characteristics of pancreatic cancer cases and controls.

	Case					Control				
	n	Age	Female *n* (%)	Diabetes *n* (%)	Mean BMI	*n*	Age	Female *n* (%)	Diabetes *n* (%)	Mean BMI
MEC										
African American	94	71.3	56 (59.6)	8 (8.5)	28.0	4,961	69.1	3,091 (62.3)	757 (15.3)	28.8
Latino	105	69.5	45 (42.9)	21 (20.0)	28.4	2,935	67.0	1,600 (54.5)	211 (7.2)	27.8
Japanese American	181	70.9	103 (56.9)	16 (8.8)	24.8	3,285	69.0	1,541 (46.9)	761 (23.2)	25.4
White	95	69.2	42 (44.2)	0 (0)	26.4	492	60.2	234 (47.6)	2 (0.4)	25.1
Native Hawaiian	43	67.0	21 (48.8)	11 (25.6)	29.6	1,753	65.4	968 (55.2)	237 (13.5)	28.6
SCCS										
African American	136	57.6	70 (51.5)	44 (32.4)	29.4	274	57.5	141 (51.5)	69 (25.2)	30.0
White	37	56.8	19 (51.4)	10 (27.0)	29.4	78	57.3	39 (50.0)	13 (16.7)	28.7

Logistic regression was used to estimate the log odds of PDAC based on binned percentiles (1%–20%, 20%–40%, 40%–60%, 60%–80%, and 80%–100%) generated using the PRS distribution among controls within each ethnic group, except for the multiethnic analysis which used the control distribution from all groups combined. Log odds of PDAC in each percentile were compared with the mid-quantile category (40%–60%). The PRS was also modeled continuously, after standardizing the score to the ethnic-specific interquartile range (IQR) among controls, except for the multiethnic analysis which used all controls. The replication and PRS analyses were stratified by ethnicity. $P < 0.05$ was used to determine statistical significance. Analysis was conducted using R 3.5.0 (30).

Results

Sample characteristics

The final analytical sample included 691 PDAC cases and 13,778 controls (518 cases and 13,426 controls from the MEC; 173 cases and 352 controls from the SCCS). Most cases were African American (230 cases/5,235 controls), followed by Japanese American (181 cases/3,285 controls), white (132 cases/570 controls), Latino (105 cases/2,935 controls), and Native Hawaiian (43 cases/1,753 controls; **Table 1**). SCCS samples were younger, had a higher prevalence of diabetes, and a higher mean BMI than MEC participants. Diabetes was common among SCCS African Americans (32.4% of cases) and MEC Native Hawaiians (25.6% of cases). A large portion of the sample was overweight or obese. SCCS African-American and white cases had a mean BMI of 31.4 kg/m^2. MEC Japanese Americans had the lowest mean BMI (24.8 kg/m^2 among cases).

SNP frequencies

All SNPs, except rs78193826 and rs35226131, had a minor allele frequency (MAF) >0.05 in the multiethnic sample. Multiple SNPs were rare in ethnic-specific groups (Supplementary Table S1), and all had similar risk allele frequencies to what is reported in prior studies (Supplementary Fig. S4). Among cases or controls combined, there were 2 SNPs in the multiethnic sample with an MAF < 0.05, 3 in whites, 3 in African Americans, 6 in Japanese Americans, 2 in Latinos, and 3 in Native Hawaiians. When considering MAF < 0.01, there were 0 SNP in the multiethnic sample, 2 in whites, 2 in African Americans, 2 in Japanese Americans, 1 in Latinos, and 1 in Native Hawaiians.

Replication analysis

Eleven of the 31 SNPs were replicated at $P < 0.05$, with consistent direction of association with that observed in the literature (Figs. 1 and 2; Supplementary Table S1). Of the replicating SNPs, 10 were

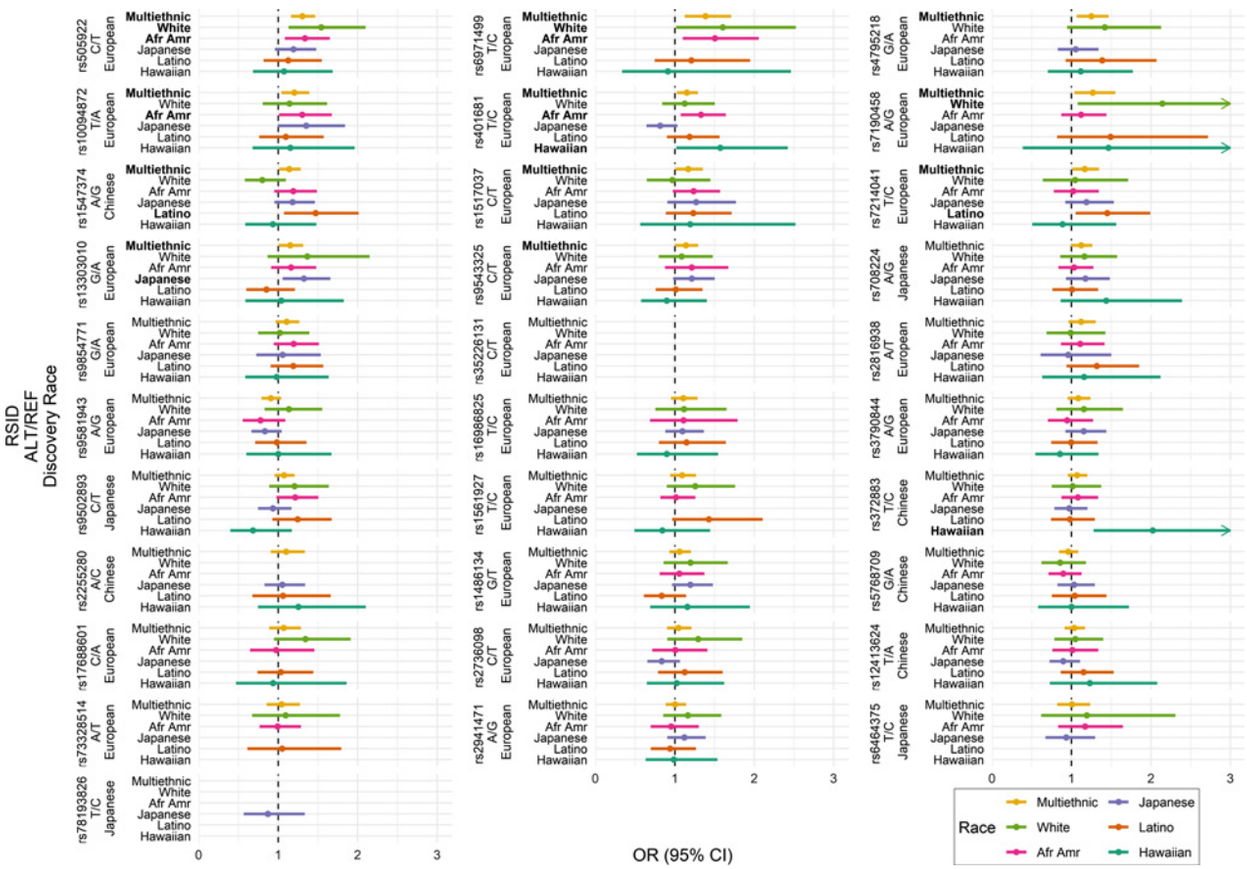

Figure 1.

Multiethnic and ethnic-specific replication analysis results for 31 SNPs identified in prior GWAS of pancreatic cancer in European, Chinese, and Japanese ancestry. Results shown on the OR scale with corresponding 95% CIs and ordered from lowest to highest *P* values from multiethnic replication analysis. Only SNPs with MAF > 0.05 are shown. ALT, alternative (risk) allele; REF, reference allele; RSID, reference SNP cluster ID.

discovered in Europeans (rs505922, rs6971499, rs4795218, rs10094872, rs401681, rs7190458, rs7214041, rs1517037, rs13303010, and rs9543325) and one (rs1547374) in Chinese. Replicating SNPs had a similar mean effect size to what is reported in the literature (mean log odds of replicating SNPs from literature: 0.20; mean log odds of replicating SNPs in multiethnic sample: 0.17). Of these 11 replicated SNPs, 8 were statistically significant in at least one ethnic group after filtering out SNPs with an MAF < 0.05 in cases or controls. Four replicated in African Americans, three in whites, one in Japanese Americans, one in Latinos, and one in Native Hawaiians, at $P < 0.05$. Within the set of 11 replicating SNPs in the multiethnic sample, with MAF > 0.05 among cases or controls, we assessed directional consistency of SNP associations with the literature. Among whites, 9 of 11 SNPs had consistent direction of effect; 11 of 11 among African Americans, 8 of 9 among Japanese Americans, 10 of 11 among Latinos, 7 of 11 among Native Hawaiians.

Of the 20 SNPs not replicating in the multiethnic sample with an MAF > 0.05, one was replicated in Native Hawaiians (rs372883; discovered in Chinese), with consistent direction of association to that observed in the literature. Within this set of nonreplicating SNPs in the multiethnic sample, with ethnic-specific MAF > 0.05, we assessed directional consistency of associations in each race/ethnic group with the literature. Among whites, 15 of 17 SNPs had consistent direction of effect; 10 of 17 among African Americans, 8 of 16 among Japanese Americans, 12 of 17 among Latinos, 7 of 16 among Native Hawaiians.

Polygenic risk score

We estimated a genetic risk score using the multiethnic effect estimates as the weight for each SNP. When comparing PRS distributions, we observed a significant difference in risk scores by case status, where cases had 0.13 higher mean PRS than controls ($P < 0.001$). In the multiethnic sample, those in the (80%–100%) risk score group had OR = 2.25 [95% confidence interval (CI), 1.73–2.92) for PDAC relative to the reference group (**Fig. 3**; Supplementary Fig. S5). The IQR-standardized PRS was significantly associated with PDAC (OR per IQR increase = 1.94; 95% CI, 1.70–2.22; P LRT = 4.092×10^{-17}). The PRS was significantly associated with PDAC risk in African Americans (OR per IQR increase = 1.91; 95% CI, 1.55–2.35; P LRT: 3.121×10^{-8}), Japanese Americans (OR = 1.46; 95% CI, 1.19–1.79; P LRT: 0.003), Latinos (OR = 1.65; 95% CI, 1.26–2.17; P LRT: 0.013), and whites (OR = 1.85; 95% CI, 1.38–2.46; P LRT: 2.937×10^{-4}). There was no significant ethnic heterogeneity of the association between PRS and PDAC in the continuous model (P heterogeneity = 0.12). We observed similar results when using alternative weighting schemes for the multiethnic analysis (Supplementary Figs. S6–S11).

Discussion

We investigated the association of GWAS-identified SNPs with pancreatic cancer risk in an ethnically diverse population. Of the 31 SNPs tested, we replicated 11 in the multiethnic sample at an alpha of 0.05. In comparison with prior replication attempts across racial

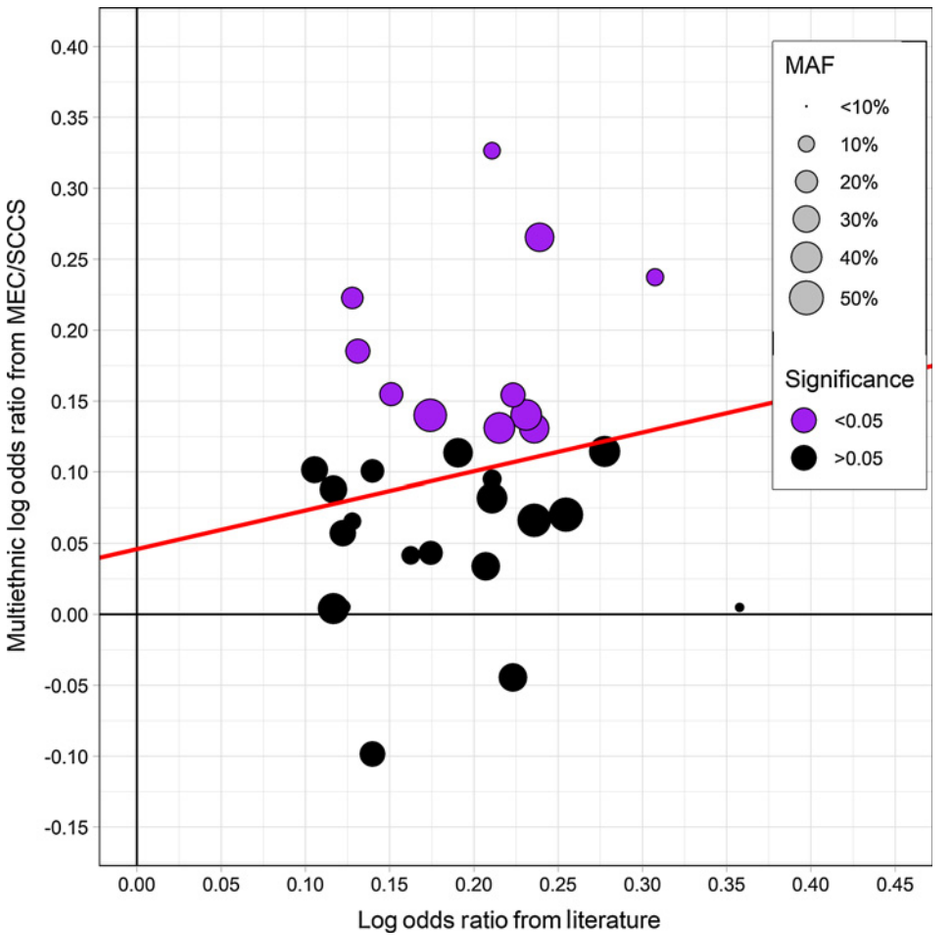

Figure 2.
Comparison between 31 replicating SNPs from multiethnic replication analysis and most recent GWAS results on the log OR scale. Point size corresponds to MAF among controls in the replication analysis. The red line represents MAF-weighted least squares fit. One point removed from figure due to extreme replication result (rs2816938, OR = 0.69).

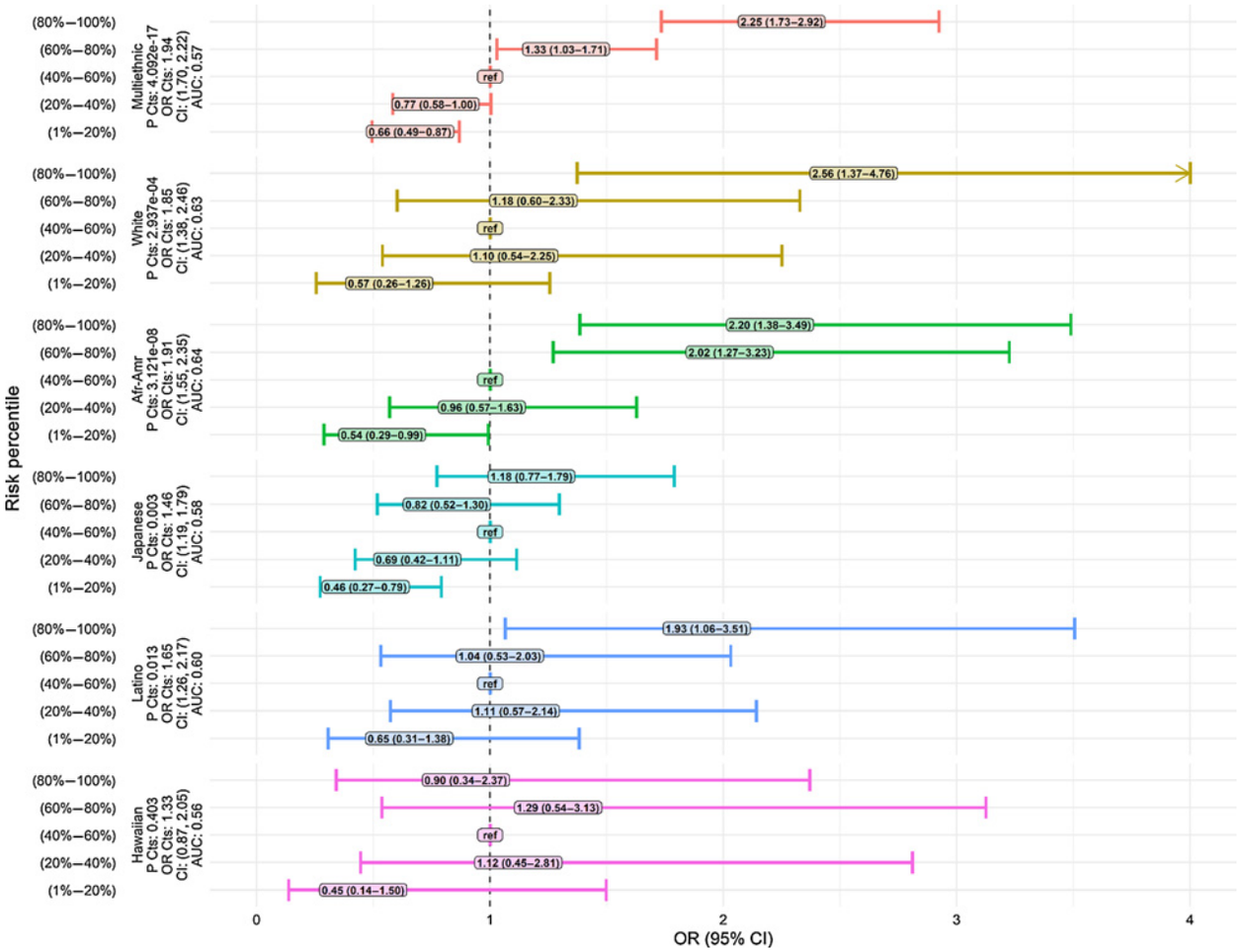

Figure 3.

Multiethnic and ethnic-specific PRS ORs and 95% CIs. Weights used from multiethnic replication analysis. Multiethnic analysis used binned risk score percentile groups from the complete, multiethnic, sample among controls. Ethnic-specific analysis used binned risk score percentile groups from the control ethnic-specific risk score distribution among controls. P Cts, *P* value from continuous PRS model; Ref, reference category used in binned regression analysis.

groups (15, 22, 23), we found a number of SNPs identified in Europeans and Asians to be associated with PDAC in a US multiethnic sample. Furthermore, we showed the potential utility of PRS with GWAS-identified risk variants for the identification of individuals at increased risk for PDAC across multiple ethnic groups.

Of the SNPs tested, the 3 least common SNPs in our multiethnic sample (MAF < 0.1 among controls) were not replicated, but 60% of the most common SNPs in our sample (MAF > 0.4) were replicated. This highlights a possible pattern between replication and allele frequencies in our multiethnic sample. Although most SNPs have been identified in GWAS of European ancestry (13–15, 18, 19, 21), only 3 of these SNPs were replicated in our white population (13, 19), the group which most similarly reflects European ancestry. This limited replication likely results from the small number of whites relative to the other ethnic groups in our study.

The most significant replicating SNP (rs505922 in *ABO*) was the first SNP identified to be associated with PDAC (13). This association was significant in whites and African Americans. In our study, this SNP was not replicated in Japanese Americans; however, it was directionally consistent with a similar effect size (OR = 1.19; 95% CI, 0.96–1.48) to prior Japanese studies (ORs range, 1.11–1.36; refs. 17, 23). The next three most significant replicating SNPs in our multiethnic sample (rs6971499, rs4795218, and rs10094872; discovered in European ancestry) have not been replicated across any race/ethnicity to our knowledge. Following these, rs401681 (*CLPTM1L*) has been replicated in Chinese (20, 22). The study that reports replication has a similar effect to ours (Wang and colleagues OR = 1.39; 95% CI, 1.11–1.74; MEC/SCCS OR = 1.15; 95% CI, 1.03–1.29); however, we observed significant heterogeneity of association by ethnic group (*P* heterogeneity = 0.01). Another frequent cross-ethnic replication from prior studies, rs9543325 (*KLF5*), was replicated in our multiethnic sample. This SNP was associated with PDAC in Japanese and Chinese (16, 17, 20, 23) with a larger effect estimate than in our multiethnic analysis and an estimate similar to our Japanese-American sample. In contrast, the single Chinese-discovered SNP (rs1547374; *TFF1*; ref. 20), which was replicated in our multiethnic sample and in the Latino subset, was not replicated in prior studies of European (15), Chinese (22), and Japanese samples (23). Lastly, rs3790844 and rs3790843 in *NR5A2* have been associated with pancreatic cancer in Europeans (15, 31) and Japanese (17, 24); however, we did not replicate

this finding. The effect estimates in MEC whites and Japanese Americans were most similar to those reported in European (15) and in Japanese ancestry (17, 24).

Reason for lack of replication between studies is likely due to limited sample size. The size of our case group is less than half the number of cases included in the first European ancestry GWAS and is only around 7% the size of the most recent European ancestry GWAS (13, 15). It is likely that the limited number of cases in our study, relative to what is seen in pancreatic cancer GWAS, resulted in a lower statistical power than required for replication of additional SNPs. A second likely factor limiting replication in our study is racial heterogeneity. Across ethnic groups, differing linkage-disequilibrium structures can lead to the tagging SNPs not being in association with the true causal SNP, resulting in lack of replication (32).

We built and tested a multiethnic genetic risk score using the previously identified 31 GWAS SNPs. The associations between PRS and PDAC risk from the multiethnic and ethnic-specific continuous models were statistically significant, except in Native Hawaiians. In the ethnic analysis, a monotonic pattern between categorical PRS and PDAC risk was clearest in African Americans. Two studies have reported a PRS analysis for PDAC (15, 23). In the most recent study, Klein and colleagues used the 22 SNPs identified in European ancestry to estimate a weighted PRS using their results and found a strong association with PDAC (15). In an earlier study, Nakatochi and colleagues first attempted to replicate 61 GWAS-identified SNPs (both significant and suggestive) and then used the 8 replicating SNPs in stepwise regression to select five independent SNPs for use in a PRS (23). They observed significant associations between the extreme PRS categories and PDAC risk.

Consistent with findings from Klein and colleagues and the Japanese ancestry PRS in Nakatochi and colleagues (15, 23), we observed an association between PRS and PDAC risk in whites and Japanese Americans. In our sensitivity analysis using weights from Klein and colleagues, we found similar performance of the PRS, with three of the four risk quantile groups differing from the reference. Both previous studies used ethnic-specific weights in their analysis which might provide a better fit in a large study. In our main analysis, we used multiethnic weights to uniformly weight SNPs across ethnicities. This was done so differences in PRS–PDAC association reflect case–control differences and not discrepancies in ethnic-specific weights which can be highly variable due to small sample sizes within some ethnic groups.

There are several strengths and limitations to this study. This is the first replication study of pancreatic cancer risk variants in a multiethnic population. Our ethnic-specific analysis is the first to produce replication estimates and show transportability of GWAS findings for multiple ethnic groups, including African Americans who have notably high pancreatic cancer incidence, yet have not been studied in the context of genetics. We leveraged existing MEC GWAS data to boost sample size which improved power needed to replicate multiple SNPs. Finally, we showed that multiethnic estimates for SNPs known to be associated with pancreatic cancer perform better than expected in both a multiethnic and ethnic-stratified PRS analysis. Limitations include our relatively small number of cases in comparison with what was included in previous GWAS, which may be responsible for some SNPs not replicating in our sample. We stratified the replication and PRS analysis by self-reported ethnicity. As observed in the principal component figures, there can be considerable variation of global ancestry within these groups.

In conclusion, we successfully replicated 11 of the 31 GWAS-identified loci in a multiethnic population. These replications provide evidence for the importance of these SNPs in understanding genetic pancreatic cancer risk in an admixed population and in understudied ethnic groups. We showed a potential value of PRS with GWAS-identified variants for the identification of individuals at increased risk for PDAC across multiple ethnic groups. Currently there is no routine screening recommended for PDAC, and thus PRS may be useful in identifying a subgroup of high-risk individuals who may benefit the most from screening with endoscopic ultrasound or MRI. Furthermore, with known modifiable risk factors (i.e., smoking, excess weight, diabetes) for PDAC, PRS may be useful for prioritizing individuals for targeted health and lifestyle-related interventions.

Disclosure of Potential Conflicts of Interest

X.-O. Shu reports grants from NIH during the conduct of the study. S.J. Pandol reports grants from NIH during the conduct of the study. W.J. Blot reports grants from NIH during the conduct of the study. L. Le Marchand reports grants from NCI (awarded to institution) during the conduct of the study. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

D. Bogumil: Formal analysis, writing–original draft, writing–review and editing. **D.V. Conti:** Formal analysis, supervision, writing–review and editing. **X. Sheng:** Data curation, formal analysis, writing–review and editing. **L. Xia:** Data curation, writing–review and editing. **X.-O. Shu:** Resources, writing–review and editing. **S.J. Pandol:** Writing–review and editing. **W.J. Blot:** Resources, data curation, funding acquisition, writing–review and editing. **W. Zheng:** Resources, data curation, writing–review and editing. **L. Le Marchand:** Resources, data curation, funding acquisition, writing–review and editing. **C.A. Haiman:** Data curation, writing–review and editing. **V.W. Setiawan:** Conceptualization, resources, formal analysis, supervision, funding acquisition, writing–original draft, project administration, writing–review and editing.

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