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Impact of Sixteen Established Pancreatic Cancer Susceptibility Loci in American Jews

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Abstract

Background—The higher risk of pancreatic cancer in Ashkenazi Jews compared to non-Jews is only partially explained by the increased frequency of *BRCA1* and *BRCA2* mutations in Ashkenazi Jews.

Methods—We evaluated the impact of 16 established pancreatic cancer susceptibility loci in a case-control sample of American Jews, largely Ashkenazi, including 406 full-Jewish pancreatic cancer patients and 2,332 full-Jewish controls, genotyped as part of the Pancreatic Cancer Cohort and Case-Control Consortium I/II (PanScan I/II), Pancreatic Cancer Case-Control Consortium (PanC4), and Resource for Genetic Epidemiology Research on Adult Health and Aging (GERA) data sets. We compared risk in full-Jewish subjects to risk in part-Jewish, non-Jewish Southern European, and in the combined non-Jewish Eastern, Northern, Southern, and Western European (non-Jewish white-European) subjects from the same data sets. Jewish ancestries were genetically identified using seeded Fast principal component analysis. Data were analyzed by unconditional logistic regression, and adjusted for age, sex, and principal components (PCs).

Results—One SNP on chromosome 13q22.1 (rs9543325, OR=1.36, 95% CI=1.16–1.58, $P=10^{-4.1}$) was significant in full-Jews. Individual ORs and minor allele frequencies were similar between Jewish and non-Jewish white-European subjects. The average ORs across the 16 pancreatic cancer susceptibility loci for full-Jewish, full- plus part-Jewish, non-Jewish Southern European, and non-Jewish white-European subjects were 1.25, 1.30, 1.31, and 1.26, respectively.

Conclusion—The 16 pancreatic cancer susceptibility loci similarly impact Jewish and non-Jewish white-European subjects, both individually and as summary odds.

Impact—These 16 pancreatic cancer susceptibility loci likely do not explain the higher risk seen in Ashkenazi Jews.

Keywords

Pancreatic Cancer; Jews; Genetics; Increased-risk

Introduction

Since the 1950s, epidemiologic studies have repeatedly found pancreatic cancer to be more frequent among Jews, particularly Ashkenazi Jews, as compared to non-Jews (1–9). Most recently, Risch and colleagues (2015) conducted a population-based case-control study and found an increased odds of pancreatic cancer for subjects reporting Jewish ancestry compared to subjects not reporting Jewish ancestry [odds ratio (OR), 1.81; 95% confidence interval (CI), (1.05–3.10)], and Eldridge and colleagues (2011) found an increased risk of pancreatic cancer mortality in Cancer Prevention Study II participants reporting Jewish religious affiliation compared to participants reporting Protestant, Catholic, Latter Day Saints, other, or no religious affiliation [risk ratio (RR), 1.43; 95% CI, (1.30–1.57)] (10, 11).

Pancreatic cancer is one of the most lethal cancers for both men and women in the United States, with a 5-year survival of less than 2% on a population basis (12). In 2015, 48,960 diagnosed cases of and 40,560 deaths from pancreatic cancer were estimated in the United States (13). Globally, in 2012, 337,872 diagnosed cases of and 330,391 deaths from pancreatic cancer were estimated to have occurred (14). Most pancreatic cancer patients present with advanced disease; however, in early disease stages patients can undergo surgical resection, which confers significant survival advantage (15).

Established risk factors for pancreatic cancer account for about half of the disease in the general population. In the United States, cigarette smoking accounts for about 20% of the disease and non-O ABO blood group explains about 19% (16–18). Other risk factors, including uncommon hereditary factors (e.g., germline mutation in *p16*, *BRCA1* and *BRCA2*, *ATM*, *PALB2*, and MMR genes), chronic pancreatitis, obesity, long-term diabetes mellitus, and *Helicobacter pylori* colonization, combined, account for around 15–20% of the disease (16, 17, 19–22). Additionally, five large-scale genome-wide association studies (GWASes) have been conducted in the white-European population: The Pancreatic Cancer Cohort and Case-Control Consortium I (PanScan I) study, the Pancreatic Cancer Cohort and Case-Control Consortium II (PanScan II) study, (23), the Pancreatic Cancer Cohort and Case-Control Consortium III (PanScan III) study, the Pancreatic Cancer Case-Control Consortium (PanC4) study, and the combined PanScan I, II, and III (PanScan I–III), PANcreatic Disease ReseArch (PANDoRA), PanC4 study. Together these studies identified 16 common low risk pancreatic cancer susceptibility loci that reached the genome-wide significance threshold: $10^{-7.3}$ (i.e. $P < 5 \times 10^{-8}$) (Supplementary Table 1) (24–28).

The increased pancreatic cancer risk among Ashkenazi Jews can be partially explained by the greater prevalence of two *BRCA1* mutations (185delAG and 5382insC) and one *BRCA2* mutation (6174delT), which together account for about 9.1% of the disease in Jews. For pancreatic cancer, the population attributable fraction (PAF) of disease in the Jewish population for the two *BRCA1* mutations is 2.40%: 1.17% total prevalence of the two *BRCA1* mutations and 3.1-fold relative risk of pancreatic cancer (19). The PAF of disease for the *BRCA2* mutation in the Jewish population is 6.74%, based on 1.29% prevalence of the *BRCA2* mutation and 6.6-fold relative risk of pancreatic cancer (19). The gene that determines ABO blood type (*ABO*) may also contribute slightly to the increased risk of pancreatic cancer among Ashkenazi Jews since the O ABO blood group frequency is lower and the B ABO blood group frequency is higher in Jews compared to white-Europeans. However, the PAF of pancreatic cancer in the Jewish population has not yet been calculated on a population basis (29, 30). Other known genetic and non-genetic risk factors for pancreatic cancer are not appreciably higher in the Jewish population compared to the non-Jewish white-European population (11).

To investigate further a genetic basis for pancreatic cancer in the Jewish population, we evaluated the impact of the 16 genome-wide significant pancreatic cancer susceptibility loci identified in the PanScan I–III, PanC4, and combined PanScan I–III, PANDoRA, PanC4 GWASes, in full-Jewish subjects, part-Jewish subjects, non-Jewish Southern European subjects, and the combined non-Jewish Eastern, Northern, Southern, and Western white-European (non-Jewish white-European) subjects. We then compared average ORs across the 16 pancreatic cancer susceptibility loci in these four populations. We chose to include non-Jewish Southern European subjects in the analysis because of all of the non-Jewish white-European populations, Southern Europeans are, genetically, the closest to Jews and historically the most genetically admixed with them (31).

Materials and methods

All subject data used in this analysis came from biosamples and data obtained from individual subjects providing written informed consent in studies that were conducted in accordance with recognized ethics guidelines (Declaration of Helsinki, International Ethical Guidelines for Biomedical Research Involving Human Subjects, Belmont Report, or U.S. Common Rule) under institutional review board approval in their respective studies.

Study data sets

PanScan I/II (accession phs000206.v4.p3), PanC4 (accession phs000648.v1.p1), and the Resource for Genetic Epidemiology Research on Adult Health and Aging (GERA) (accession phs000674.v1.p1) data sets were obtained from the database of Genotypes and Phenotypes (dbGaP) (32). Information on age, sex, case/control status, and genotype was available from all three dbGaP data sets. For the GERA data set, only subjects genotyped on the Affymetrix Axiom Genome-Wide EUR array (white-European subjects) without cancer diagnoses were considered for inclusion in our study population. PanScan I/II and PanC4 contributed cases and controls to our study population, while GERA contributed only controls.

Reference marker data sets

Three sub-studies from PanScan I/II and PanC4 were obtained with information on genotypes and self-reported race and ethnicity. In total, 311 self-reported white-European (including Jewish or half-Jewish), black, or Asian subjects from the Yale Connecticut Pancreas (Yale) study included in PanScan I/II and PanC4 (24, 25, 27), 27 self-reported Jewish or half-Jewish subjects from the Johns Hopkins University (JHU) study included in PanC4 (27), and 107 subjects with self-reported number of Jewish grandparents from the Memorial Sloan Kettering Cancer Center (MSKCC) study included in PanC4 (27), were used as reference marker subjects to help genetically identify the full-Jewish, part-Jewish, non-Jewish Southern European, and non-Jewish white-European subjects on principal component (PC) plots. Information on subjects' parents' place of birth was included in the Yale study and was used to categorize non-Jewish white-European subjects into Eastern, Northern, Southern, and Western Europeans (Supplementary Table 2).

Imputation data sets

The publicly available 1000 Genomes Project Phase 3 (October 2014 release) data set and the Ashkenazi Genome Consortium (TAGC) data set (European Genome-phenome Archive Study ID: EGAS00001000664) were used as reference panels for haplotype estimations (pre-phasing) and genotype imputation (33, 34).

Quality control (QC)

Subjects from PanScan I were genotyped on the Illumina HumanHap550 Infinium array, subjects from PanScan II were genotyped on the Illumina Human610-Quad array, subjects from PanC4 were genotyped on the Illumina HumanOmniExpressExome array, and subjects from GERA were genotyped on the Affymetrix Axiom Genome-wide EUR array. QC was performed separately using high thresholds for subject genotyping completion and variant call rate for each of the four genotyping platforms in PLINK v1.90-beta (35).

Sample and subject QC—Sample replicates, failed samples, subjects with <98% genotyping completion, subjects with missing sex information, indeterminable X chromosome heterozygosity, or a discordance in reported vs. genotyped sex (reported females with >0.25 and reported males with <0.80 X chromosome heterozygosity), and related subjects ($\hat{\pi} < 0.20$) were removed from the data sets. For a pair of related subjects on the Illumina HumanHap550 Infinium array, the Illumina Human610-Quad array, and the Illumina HumanOmniExpressExome array, the control subject was removed in a case-control comparison and one subject was randomly chosen to be removed in a case-case or control-control comparison. For a pair of related subjects on the Axiom Genome-wide EUR array, the younger subject was removed. Finally, subjects across the four platforms were combined, and 55 seemingly related subjects between PanScan I/II and PanC4, 61 between PanScan I/II and GERA, and 12 between PanC4 and GERA were identified and removed ($\hat{\pi} < 0.20$). Related subjects between PanScan I/II and PanC4 were removed from the PanC4 data set, and related subjects between PanScan I/II and GERA, and PanC4 and GERA were removed from the GERA data set. The numbers of samples and subjects excluded from the genotyping arrays at each QC step are listed in Supplementary Table 3a.

Variant QC—Variants with duplicate positions, call rates <98%, extreme Hardy Weinberg equilibrium departures in controls ($p < 10^{-7}$), monomorphic variants in either cases or controls, copy number variants, and variants not in autosomal chromosomes were removed. Only single nucleotide polymorphisms (SNPs) remained after variant QC. After QC, there were 530,771 SNPs on the Illumina HumanHap550 Infinium array, 553,743 SNPs on the Illumina Human610-Quad array, 804,262 SNPs on the Illumina HumanOmniExpressExome array, and 596,652 SNPs on the Affymetrix Axiom Genome-wide EUR array. The numbers of variants excluded from the genotyping arrays at each QC step are listed in Supplementary Table 3b.

Reference marker sample, subject, and variant QC—QC was done separately for the Yale reference marker subjects in PanScan I/II genotyped on the Illumina Human610-Quad array, Yale reference marker subjects in PanC4 genotyped on the Illumina HumanOmniExpressExome array, JHU reference marker subjects in PanC4 genotyped on the Illumina HumanOmniExpressExome array, and MSKCC reference marker subjects in PanC4 genotyped on the Illumina HumanOmniExpressExome array. QC procedures discussed above in the *Sample and subject QC* and *Variant QC* section were applied to the Yale, JHU, and MSKCC reference marker data sets.

Fast principal component analysis (FastPCA)

FastPCA is an accurate approximation of exact PCA and can be used when exact PCA cannot be performed because of sample size limitations ($N < 10,000$ subjects). Since Jewish subjects were identified in a sample of over 50,000 subjects, exact PCA ran out of memory and FastPCA had to be used (36).

Jewish subjects—Four FastPCAs were sequentially conducted with all post-QC 80,772 genotyped SNPs common to the Illumina HumanHap550 Infinium, Illumina Human610-Quad, Illumina HumanOmniExpressExome, and Affymetrix Axiom Genome-wide EUR arrays, in order to identify the PanScan I/II, PanC4, and GERA (PanScan/PanC4/GERA) full- or part-Jewish subjects (Supplementary Figure 1). FastPCA was run in EIGENSOFT v6 (36). First, FastPCA was performed on 55,930 PanScan/PanC4/GERA subjects of various races and ethnicities, including 44 self-reported black, seven Asian, and 78 Jewish or half-Jewish reference marker subjects from the Yale study. The FastPCA PC2 vs. PC1 plot enabled visualization of the PanScan/PanC4/GERA subjects (Supplementary Figure 2a). In total, 54,829 white-European subjects to the right of the diagonal line in Supplementary Figure 2a were retained, and a second FastPCA was run with these white-European subjects, plus 78 Jewish or half-Jewish reference marker subjects from the Yale study. FastPCA PC2 vs. PC1 was again plotted to visualize the white-European subjects (Supplementary Figure 2b). From this, 47,545 white-European subjects to the left of the diagonal line in Supplementary Figure 2b were retained, and a third FastPCA was run with these white-European subjects and the 78 Jewish or half-Jewish reference marker subjects, plus 29 Eastern European, 48 Northern European, 65 Southern European, and 12 Western non-Jewish white-European reference marker subjects from the Yale study, 107 full- or part-Jewish reference marker subjects from the MSKCC study, and 27 Jewish or half-Jewish reference marker subjects from the JHU study. PC2 vs. PC1 from FastPCA was plotted to

visualize the spread between the full-Jewish, part-Jewish, and non-Jewish white European subjects (Supplementary Figure 2c). In total, 4,657 full- or part-Jewish subjects to the left of the two intersecting diagonal lines in Supplementary Figure 2c were retained, and a fourth FastPCA was run on these 4,657 full- or part-Jewish subjects and 78 Jewish or half-Jewish reference marker subjects from the Yale study, 105 full- or part-Jewish reference marker subjects from the MSKCC study, and 26 Jewish or half-Jewish reference marker subjects from the JHU study. PC2 vs PC1 from FastPCA was again plotted to visualize the spread among the full-Jewish, 3/4 Jewish, 1/2 Jewish, and 1/4 Jewish subjects (Figure 1). All lines were placed on these four FastPCA plots based on location of the reference marker subjects and where subject clusters thinned.

Non-Jewish Southern European subjects—Three FastPCAs were sequentially conducted with all post-QC 80,772 common genotyped SNPs in order to identify the PanScan/PanC4/GERA non-Jewish Southern European subjects (Supplementary Figure 1). The first two analyses were run as described above to visualize white-European subjects (Supplementary Figures 2a and 2b). The 4,657 full- or part-Jewish subjects (Figure 1) were removed from 54,829 white-European subjects (Supplementary Figure 2b) and a third FastPCA was run on 50,172 non-Jewish white-European subjects and 29 Eastern European, 48 Northern European, 65 Southern European, 12 Western non-Jewish white-European, and 2 non-Jewish Middle Eastern reference marker subjects from the Yale study. PC2 vs. PC1 from FastPCA was plotted to identify non-Jewish Southern European subjects (Supplementary Figure 2d). Again, all lines were placed on FastPCA plots based on location of the reference marker subjects and where subject clusters thinned.

Study Subjects

Full-Jewish, part-Jewish, non-Jewish Southern European, and non-Jewish white-European subjects were visually identified on FastPCA plots (Figure 1, Supplementary Figures 2a–2d). In the individual site studies, reference marker subjects reporting ancestry variously as “Jewish” or “half-Jewish” or as number of Jewish grandparents, facilitated identification of the relevant regions on the FastPCA plots. In total, 406 full-Jewish pancreatic cancer cases and 2,332 full-Jewish controls, 133 part-Jewish pancreatic cancer cases and 1,785 part-Jewish controls, 585 non-Jewish Southern European pancreatic cancer cases and 3,371 non-Jewish Southern European controls, and 6,858 non-Jewish white-European pancreatic cancer cases and 43,310 non-Jewish white-European controls, all with age, sex, case/control status, and genotype information, were included in the sub-group analyses.

SNP selection

The 16 pancreatic cancer susceptibility loci that reached the genome-wide significance threshold ($P < 10^{-7.3}$) in the PanScan I–III, PanC4, and combined PanScan I–III, PANDORA, PanC4 GWASes, were examined in the sub-group analyses (Supplementary Table 1).

Association analysis

Pre-phasing, using SHAPEIT v2, and genotype imputation, using IMPUTE v2, were performed separately for white-European subjects genotyped on the Illumina HumanHap550 Infinium array, the Illumina Human610-Quad array, the Illumina

HumanOmniExpressExome array, and the Affymetrix Axiom Genome-wide EUR array. (Supplementary Figure 1) (37, 38). Prior to imputation, variants that could not map from human genome version 18 (hg18) to human genome version 19 (hg19) were removed. The manufacturers' annotation files and the University of California Santa Cruz (UCSC) genome browser were used to align genotypes for imputation; therefore, variants not in these files were removed (N, Illumina HumanHap550 Infinium array = 1,745; N, Illumina Human610-Quad array = 2071; N, Illumina HumanOmniExpressExome array = 21,488; N, Affymetrix Axiom Genome-wide EUR array = 6,895) (39). Exome labeled variants were also removed from the Illumina HumanOmniExpressExome array because of their poor representation in the 1000 Genomes Project Phase 3 and TAGC reference panels (N = 132,930). The average information metric (37) for the 9 imputed SNPs on the Illumina HumanHap550 Infinium array, the 9 imputed SNPs on the Illumina Human610-Quad array, the 8 imputed SNPs on the Illumina HumanOmniExpressExome, and the 12 imputed SNPs on the Affymetrix Axiom Genome-wide EUR array, were 0.929, 0.929, 0.937, and 0.892, respectively. Information metrics for individually imputed SNPs are listed in Supplemental Tables 4a–4d. IMPUTE genotype probabilities for the 16 pancreatic cancer susceptibility loci were converted to genotypes using a hard call threshold of 0.49999. Each SNP genotype was coded as a count of variant alleles. Ethnicity specific European minor allele frequencies (MAFs) for the 16 pancreatic cancer susceptibility loci genotyped on the Affymetrix array (control-only subjects) were confirmed to be similar to the ethnic specific European MAFs on the Illumina arrays (case and control subjects) (Supplementary Tables 4a–4d). All association analyses were conducted in PLINK v1.90-beta using unconditional logistic regression. The full-Jewish, part-Jewish, full- plus part-Jewish, and non-Jewish Southern European populations were adjusted for age (in 10-year categories), sex, and 6 sub-group specific PCs from exact principal component analysis (PCA). EIGENSOFT v6 ran out of memory when running exact PCA for the non-Jewish white-European population, and subsequently this population was adjusted for age (in 10-year categories), sex, and 6 PCs from the non-Jewish white-European FastPCA. SNP associations were considered significant at the Bonferroni correction for multiple comparisons level, $P < 0.003$ ($0.05/16$ SNPs).

An average OR in controls was estimated according to their modeled covariates (10) by calculating a weighted average,

$$\text{Average OR} = \frac{1}{n} \sum_i w_i \exp\left(\sum_j c_j \beta_j x_{ij}\right),$$

where n =total number of controls, the c_j s are used to select the terms of interest in the calculation, allowing adjustment of the model for potential confounders (0 or 1), the sum on i is over all n controls, x_{ij} =the number of variant alleles per genotype (0, 1, or 2), β_j =log(OR), the sum on j is over the 16 pancreatic cancer susceptibility loci, and $w_i=1$, under the assumption that the controls comprise approximately representative samples of their underlying populations.

A PAF was calculated for the full-Jewish population and compared to the PAF for the non-Jewish white-European population according to the prevalence of non-O ABO blood groups.

Blood groups (A, B, AB, and O) were determined using the two SNPs rs8176746 and rs505922 (17, 40), and analyses were done in R v3 (41).

Results

For 16 a priori pancreatic cancer susceptibility loci, we used a threshold of statistical significance $P=0.05/16=0.003$. At this threshold, one of the 16 pancreatic cancer susceptibility loci was significantly associated with risk in the full-Jewish subjects: 13q22.1 (rs9543325, OR=1.36, 95% CI=1.16–1.58, $P=10^{-4.1}$). For the remaining 15 susceptibility loci, 12 of the point estimates and directions of association were consistent with the PanScan I–III, PanC4, and combined PanScan I–III, PANDoRA, PanC4 GWASes: chr9q34.2/rs505922, chr1q32.1/rs3790844, chr5p15.33/rs451360, chr7q32.3/rs6971499, chr16q32.1/rs7190458, chr17q24.3/rs11655237, chr2p14/rs1486134, chr7p14.1/rs17688601, chr3q28/rs9854771, chr1q32.1/rs2816938, and chr8q24.21/rs10094872; two of the point estimates and directions of association were opposite: chr13q12.2/rs9581943 and chr5p15.33/rs35226131; and one point estimate was essentially null: chr5p15.33/rs2736098 (see Table 1 for ORs and P-values, Supplementary Table 4a).

We compared association results in full-Jewish subjects between the genotype threshold method (above) in PLINK v1.09-beta and the genotype dosage method (below) in SNPTEST v2 (42). We found similar ORs and P-values between these two association analysis methods (OR=1.21, 95% CI=1.04–1.41, $P=0.016$ for rs505922 and OR=1.36, 95% CI=1.17–1.58, $P=10^{-4.2}$ for rs9543325, using the genotype dosage association method) (Table 1).

For sensitivity purposes, when we moved the line that separates full-Jewish from part-Jewish subjects on the FastPCA plot in Figure 1 and recalculated full-Jewish subjects' ORs and P-values to include or exclude ~30 full-Jews, we found the results to be consistent with the original full-Jewish subjects' analysis (OR=1.23, 95% CI=1.05–1.43, $P=10^{-2.1}$ and OR=1.21, 95% CI=1.03–1.41, $P=0.018$ for rs505922 with ~+/- 30 full-Jewish subjects; and OR=1.35, 95% CI=1.16–1.57, $P=10^{-4.0}$ and OR=1.37, 95% CI=1.17–1.59, $P=10^{-4.2}$ for rs9543325 with ~+/- 30 full-Jewish subjects).

In part-Jewish subjects, one of the 16 pancreatic cancer susceptibility loci was significantly associated with risk: 5p15.33 (rs451360, OR=1.53, 95% CI=1.17–1.99, $P=10^{-2.7}$). For the remaining 15 susceptibility loci, 12 of the point estimates and directions of association were consistent with the PanScan I–III, PanC4, and combined PanScan I–III, PANDoRA, PanC4 GWASes: 9q34.2/rs505922, 13q22.1/rs9543325, 1q32.1/rs3790844, 5p13.33/rs2736098, 7q32.3/rs6971499, 16q23.1/rs7190458, 13q12.2/rs9581943, 22q12.1/rs16986825, 17q24.3/rs11655237, 2q14/rs1486134, 1q32.1/rs2816938, and 8q24.21/rs10094872; and three of the point estimates and directions of association were opposite: 7p14.1/rs17688601, 3q28/rs9854771, and 5p15.33/rs35226131 (see Table 1 for ORs and P-values, Supplementary Table 4b).

Two of the 16 pancreatic cancer susceptibility loci were significantly associated with risk in the non-Jewish Southern European subjects: 5p15.33 (rs451360, OR=1.35, 95% CI=1.18–1.54, $P=10^{-5.1}$) and 17q24.3 (OR=1.34, 95% CI=1.13–1.61, $P=10^{-3.1}$). For the remaining 14

susceptibility loci, 13 of the point estimates and directions of association were consistent with the PanScan I–III, PanC4 and combined PanScan I–III, PANDoRA, PanC4 GWASes: 9q34.2/rs505922, 9q34.2/rs9543325, 1q32.1/rs3790844, 7q32.3/rs6971499, 16q23.1/rs7190458, 13q12.2/rs9581943, 22q12.1/rs16986825, 2p14/rs1486134, 7p14.1/rs17688601, 3q28/rs9854771, 1q32.1/rs2816938, 8q24.21/rs10094872, and 5p13.33/rs35226131; and 5p15.33/rs2736098 had an opposite point estimate and direction of association (see Table 1 for ORs and P-values, Supplementary Table 4c).

Fifteen of the 16 pancreatic cancer susceptibility loci identified in the PanScan I–III, PanC4, and combined PanScan I–III, PANDoRA, PanC4 GWASes were significantly associated with pancreatic cancer risk in the non-Jewish white-European subjects (the SNP rs35226131 was not significantly associated with pancreatic cancer) (Table 1, Supplementary Table 4d).

Individual ORs and MAFs were similar between Jewish and non-Jewish white European subjects. The average ORs over the 16 SNPs in the four sub-groups were similar: in the full-Jewish subjects the average OR was 1.25, in the full- plus part-Jewish subjects it was 1.30, in the non-Jewish Southern European subjects it was 1.31, and in the non-Jewish white-European subjects it was 1.26.

When the published point estimates from the PanScan I–III, PanC4, and combined PanScan I–III, PANDoRA, PanC4 GWASes were compared to the point estimates from the all white-European subjects (Jewish and non-Jewish European), 15 of the 16 pancreatic cancer susceptibility loci had comparable ORs and P-values (the SNP rs35226131 was not significantly associated with pancreatic cancer) (Supplementary Table 1).

The expected increased risk of pancreatic cancer according to non-O ABO blood groups in the full-Jewish population compared to the non-Jewish white-European population was 2%. The PAF for pancreatic cancer was 19.4% in the full-Jewish population and 17.4% in the non-Jewish white-European population according to the prevalence of non-O ABO blood groups, based on a 0.65 prevalence of the non-O ABO blood groups in the full-Jewish population, a 0.57 prevalence in the non-Jewish white-European population, and a 1.37-fold relative odds of pancreatic cancer.

Discussion

To our knowledge, this is the first study to examine the 16 pancreatic cancer susceptibility loci found in the white-European population in the higher-risk Jewish population, and the first study to use PCs to identify and distinguish part- or full-Jews from other European populations for analyses. We are confident that the overwhelming majority of full- or part-Jews in our study are of Ashkenazi descent since participants from the sub-studies included in our study were recruited in the United States, where some 90% of Jews are of Ashkenazi descent (43). Though infrequent in a United States Jewish population, there may be a few Jews of Spanish/Portuguese Jewish descent included in the full- or part-Jewish clusters identified by FastPCA plots. Other Jews, such as Yemenite, Ethiopian, and Iranian Jews are not genetically close enough to be included in these Jewish clusters (44, 45).

Our results show an association between 13q22.1 (rs9543325) and risk of pancreatic cancer among full-Jewish subjects. While we attempted to obtain data sets with as many cases of pancreatic cancer as possible, our study was somewhat underpowered to detect associations of modest effect (OR~1.15) and MAF (~0.30) in the full-Jewish sub-group analysis. A power analysis with the full-Jewish sub-group sample size of 406 pancreatic cancer cases and 2,332 controls showed this sub-group analysis to have >70% power to detect an association size of 1.31 for a SNP with a MAF >0.35 (P=0.003) (46). Nevertheless, 12 of the 15 SNPs that were underpowered to detect such association showed consistent point estimates and directions of association compared to the published results in the larger original studies.

For pancreatic cancer, we calculated a slightly higher expected risk increase (2%) attributable to the higher prevalence of non-O ABO blood groups in the full-Jewish population compared to the non-Jewish white-European population based on the SNP rs505922, which is in high linkage disequilibrium with the functional SNP rs8176719 on 9q34.2. None of the other 15 white-European pancreatic cancer susceptibility loci have been explored more in depth in the Jewish population or have established associations with other diseases in the Jewish population (47).

Across ethnicity, our results do not show a consistent pattern in the ORs for the 16 pancreatic cancer susceptibility loci, though we might have expected them to progress from non-Jewish white-European subjects (genetically furthest away from the full-Jewish subjects) to the full-Jewish subjects, with the non-Jewish Southern European subjects (genetically closest to full-Jewish subjects of all non-Jewish white-European subjects) and the part-Jewish subjects (genetically closest to the full-Jewish subjects) in between. This lack of a consistent trend may be because part-Jewish subjects are exogamously mixed more with non-Jewish Eastern, Northern, and Western Europeans than with non-Jewish Southern Europeans, as seen in Supplementary Figure 2c, as well as the small numbers and wider confidence intervals in the part-Jewish subjects.

Finally, the average OR of the 16 pancreatic cancer susceptibility loci did not show any differences in summary odds of pancreatic cancer among the full-Jewish, full- plus part-Jewish, non-Jewish Southern European, and non-Jewish white-European subjects, suggesting that other variants should be investigated for increasing the risk of pancreatic cancer in the Jewish population. Further work needs to be done to explore the association between other variants and pancreatic cancer in the Jewish population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

OR

odds ratio

CI

confidence interval

RR

risk ratio

GWAS

genome-wide association study

PanScan I

Pancreatic Cancer Cohort and Case-Control Consortium I

PanScan II

Pancreatic Cancer Cohort and Case-Control Consortium II

PanScan III

Pancreatic Cancer Cohort and Case-Control Consortium III

PanC4

Pancreatic Cancer Case-Control Consortium

PanScan I-III

PanScan I, II, and III

PANDoRA

PANcreatic Disease ReseArch Consortium

PAF

population attributable fraction

non-Jewish white-European

non-Jewish Eastern, Northern, Southern, and Western white-European

GERA

Genetic Epidemiology Research on Adult Health and Aging study

dbGaP

database of Genotypes and Phenotypes

JHU

Johns Hopkins University

Yale

Yale Connecticut Pancreas study

MSKCC

Memorial Sloan Kettering Cancer Center

PC

principal component

TAGC

the Ashkenazi Genome Consortium

QC

quality control

SNP

single nucleotide polymorphism

UCSC

University of California Santa Cruz, FastPCA, fast principal component analysis

PanScan/PanC4/GERA

PanScan I/II, PanC4, and GERA

MAF

minor allele frequency

PCA

principal component analysis

NCBI

National Center for Biotechnology Information

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Figure 1.

FastPCA plot of components 2 v. 1 for 4,657 PanScan/PanC4/GERA Jewish subjects and full- or part-Jewish reference marker subjects. The left vertical line demarcates separation between 1/4 Jewish and 1/2 or 3/4 Jewish subjects. The right vertical line demarcates separation between 1/2 or 3/4 Jewish subjects and full-Jewish subjects.

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Table 1

Sub-group analysis in PanScan/PanC4/GERA full-Jewish, part-Jewish, non-Jewish Southern European, and non-Jewish white-European subjects for 16 previously reported pancreatic cancer susceptibility loci in the PanScan I–III, PanC4, and combined PanScan I–III, PANDoRA, PanC4 GWASes

SNP (alleles) ^a Chromosome ^b Position ^c Gene ^d	Study	PanScan/PanC4/GERA full-Jewish subjects ^e			PanScan/PanC4/GERA part-Jewish subjects			PanScan/PanC4/GERA non-Jewish Southern European subjects			PanScan/PanC4/GERA non-Jewish white-European subjects		
		Odds Ratio (95% CI) ^f	P	European MAF (Cases, Controls) ^g	Odds Ratio (95% CI)	P	European MAF (Cases, Controls)	Odds Ratio (95% CI)	P	European MAF _v (Cases, Controls)	Odds Ratio (95% CI)	P	European MAF (Cases, Controls)
rs505922 (C,T) 9q34.2 136149229 <i>ABO</i>	PanScan I	1.21 (1.04–1.41)	0.014	0.445, 0.394	1.32 (1.01–1.73)	0.043	0.417, 0.359	1.18 (1.04–1.35)	0.012	0.384, 0.345	1.24 (1.19–1.29)	10 ^{–28.1}	0.394, 0.335
rs9543325 (C,T) 13q22.1 73916628 <i>KLF5, KLF12</i>	PanScan II	1.36 (1.16–1.58)	10 ^{–4.1}	0.566, 0.493	1.03 (0.80, 1.33)	0.81	0.440, 0.428	1.18 (1.03–1.34)	0.14	0.463, 0.416	1.24 (1.19–1.28)	10 ^{–28}	0.416, 0.367
rs3790844 (G,A) 1q32.1 200007432 <i>NR5A2</i>	PanScan II	0.82 (0.68–0.99)	0.039	0.208, 0.239	0.76 (0.54–1.06)	0.10	0.184, 0.236	0.81 (0.69–0.95)	0.010	0.175, 0.213	0.81 (0.77–0.85)	10 ^{–19.1}	0.200, 0.232
rs451360 (T,C) ^h 5p15.33 1322087 <i>CLPTMIL- TERT</i>	PanScan II	1.21 (1.04–1.41)	0.014	0.478, 0.429	1.53 (1.17–1.99)	10 ^{–2.7}	0.500, 0.406	1.35 (1.18–1.54)	10 ^{–5.1}	0.500, 0.429	1.36 (1.31–1.41)	10 ^{–57.1}	0.488, 0.413
rs2736098 (T,C) 5p15.33 1294086 <i>CLPTMIL- TERT</i>	PanScan III	1.00 (0.84–1.18)	0.96	0.272, 0.276	0.92 (0.68–1.25)	0.59	0.241, 0.264	1.09 (0.94–1.26)	0.25	0.280, 0.261	0.92 (0.88–0.96)	10 ^{–3.7}	0.243, 0.260
rs6971499 (C,T) 7q32.3 130680521 <i>LINC-PINT</i>	PanScan III	0.94 (0.75–1.16)	0.55	0.138, 0.146	0.80 (0.55–1.17)	0.25	0.124, 0.157	0.76 (0.62–0.94)	0.010	0.103, 0.129	0.82 (0.78–0.87)	10 ^{–12.2}	0.129, 0.153
rs7190458 (A,G) 16q23.1 75263661 <i>BCAR1</i>	PanScan III	1.41 (1.03–1.92)	0.034	0.0653, 0.0482	1.75 (1.07–2.87)	0.026	0.0790, 0.0491	1.12 (0.84–1.50)	0.42	0.0521, 0.0488	1.20 (1.11–1.30)	10 ^{–5.1}	0.0578, 0.0493
rs9581943 (A,G) 13q12.2 28493997 <i>PDX1</i>	PanScan III	0.93 (0.79–1.09)	0.35	0.334, 0.347	1.26 (0.97–1.65)	0.086	0.444, 0.378	1.16 (1.02–1.32)	0.019	0.459, 0.422	1.13 (1.09–1.17)	10 ^{–10.2}	0.439, 0.410
rs16986825 (T,C) 22q12.1 29300306 <i>ZNRF3</i>	PanScan III	1.17 (0.96–1.43)	0.11	0.182, 0.161	1.57 (1.14–2.16)	10 ^{–2.2}	0.229, 0.160	1.01 (0.85–1.19)	0.94	0.191, 0.180	1.13 (1.07–1.19)	10 ^{–5.9}	0.169, 0.152

SNP (alleles) ^a Chromosome ^b Position ^c Gene ^d	Study	PanScan/PanC4/GERA full-Jewish subjects ^e			PanScan/PanC4/GERA part-Jewish subjects			PanScan/PanC4/GERA non-Jewish Southern European subjects			PanScan/PanC4/GERA non-Jewish white-European subjects		
		Odds Ratio (95% CI) ^f	P	European MAF (Cases, Controls) ^g	Odds Ratio (95% CI)	P	European MAF (Cases, Controls)	Odds Ratio (95% CI)	P	European MAF _v (Cases, Controls)	Odds Ratio (95% CI)	P	European MAF (Cases, Controls)
rs11655237 (T,C) 17q24.3 70400166 <i>LINC00673</i>	PanC4	1.38 (1.08–1.77)	0.011	0.110, 0.0819	1.25 (0.86–1.82)	0.25	0.132, 0.107	1.34 (1.13–1.61)	10 ^{−3.1}	0.160, 0.122	1.24 (1.18–1.31)	10 ^{−14.7}	0.138, 0.113
rs1486134 (G,T) 2p14 67639769 <i>ETAA1</i>	PanC4	1.09 (0.92–1.30)	0.31	0.257, 0.238	1.02 (0.76–1.35)	0.92	0.274, 0.262	1.23 (1.07–1.42)	10 ^{−2.4}	0.287, 0.246	1.09 (1.04–1.13)	10 ^{−4.2}	0.304, 0.285
rs17688601 (A,C) 7p14.1 40866663 <i>SUGCT</i>	PanC4	0.97 (0.82–1.15)	0.70	0.246, 0.257	1.11 (0.84–1.46)	0.46	0.301, 0.275	0.91 (0.78–1.05)	0.18	0.277, 0.293	0.87 (0.83–0.91)	10 ^{−10.2}	0.241, 0.266
rs9854771 (A,G) 3q28 189508471 <i>TP63</i>	PanC4	0.78 (0.67–0.92)	10 ^{−2.5}	0.298, 0.350	1.01 (0.77–1.32)	0.96	0.353, 0.350	0.95 (0.83–1.08)	0.41	0.348, 0.358	0.89 (0.86–0.93)	10 ^{−8.4}	0.337, 0.365
rs2816938 (A,T) 1q32.1 199985368 <i>NR5A2</i>	PanScan I–III PANDoRA, PanC4	1.09 (0.91–1.30)	0.34	0.245, 0.228	1.27 (0.95–1.68)	0.10	0.271, 0.221	1.11 (0.96–1.28)	0.16	0.259, 0.237	1.21 (1.16–1.26)	10 ^{−17.9}	0.263, 0.227
rs10094872 (T,A) 8q24.21 128719884 <i>MYC</i>	PanScan I–III, PANDoRA, PanC4	1.20 (1.03–1.41)	0.021	0.385, 0.343	1.36 (1.05–1.77)	0.020	0.406, 0.334	1.07 (0.94–1.22)	0.32	0.347, 0.336	1.14 (1.10–1.18)	10 ^{−10.8}	0.393, 0.360
rs35226131 (T,C) 5p15.33 1295373 <i>CLPTMIL-TERT</i>	PanScan I–III, PANDoRA, PanC4	1.31 (0.76–2.26)	0.33	0.0209, 0.0152	1.26 (0.53–3.02)	0.60	0.0225, 0.0202	0.58 (0.33–1.03)	0.62	0.0120, 0.0190	0.85 (0.74–0.97)	0.017	0.0184, 0.0210

^aEuropean minor allele, reference allele.

^bCytogenetic region according to National Center for Biotechnology Information (NCBI) Human Genome Build 37 (hg19).

^cSNP position according to NCBI Human Genome Build 37 (hg19).

^dClosest RefSeq genes.

^eAllelic odds ratio and 95% confidence interval adjusted for age, sex, and PC1-PC6.

^gEuropean MAF, European minor allele frequency.

^hThis locus was originally tagged by401681, but has now been fine mapped to rs451360 and correlated variants.