CORIELL
PERSONALIZED MEDICINE
COLLABORATIVE

Multi-Variant Risk Reporting in the Coriell Personalized Medicine Collaborative (CPMC®) Research Study

APPENDIX: Pancreatic Cancer

Single Nucleotide Polymorphism (SNP) Identification

To be considered for use in multigenic risk reporting for pancreatic cancer we required each SNP to: 1) show statistically significant association with pancreatic cancer after correction for multiple testing and be replicated in at least one independent population sample (Peterson et al. 2010; Wu et al. 2011), 2) be unlinked with all other SNPs in the final model (R2 < 0.2), 3) be captured in the current version of the Affymetrix 6.0 Genotyping Array, 4) pass Coriell's internal SNP genotyping quality controls, and 5) be approved by the ICOB.

SNPs associated with pancreatic cancer were initially identified in the NIH GWAS catalog (www.genome.gov/gwastudies). References from this catalog were then used in parallel with PubMed searches to explore the extent of the literature support for association. In this case, variants were evaluated in multiple population samples with consistent results. We therefore find no reason not to report RR values from the same model to all CPMC participants.

Model

The CPMC model of pancreatic cancer relative risk (RR), calculated via REGENT, includes three ICOB-approved, CLIA-validated SNPs captured by the current Affy 6.0 Genotyping Platform: rs3790844, rs401681, rs4885093 (also see Table 1 for input parameters). We used a prevalence estimate of 0.000113. Odds ratios from the listed citations were converted to relative risk (RR) values as described in the white paper. For variants with minor allele frequencies > 0.50, we inverted RR values as described in the white paper.

Table 1.

SNP	MAF	Ncase	Ncontrol	OR_het	OR_hom	Citation
rs3790844	0.24	3532	3641	0.75	0.64	Peterson et al. 2010
rs401681	0.45	3532	3642	1.20	1.41	Peterson et al. 2010
rs4885093	0.44	3584	4868	1.25	1.50	Wu et al. 2011

Evaluation

Figure 1 displays excellent consistency of categorical boundaries determined by REGENT.model across 100 simulations. Figure 2 displays excellent consistency of the proportion of individuals assigned to a given category by REGENT.model.

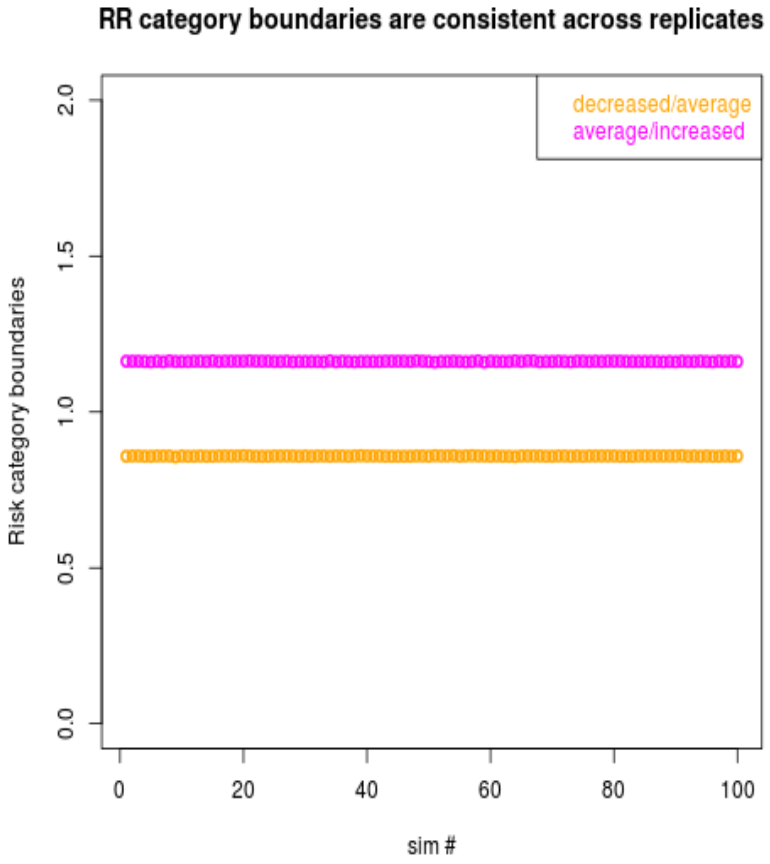

Figure 1.

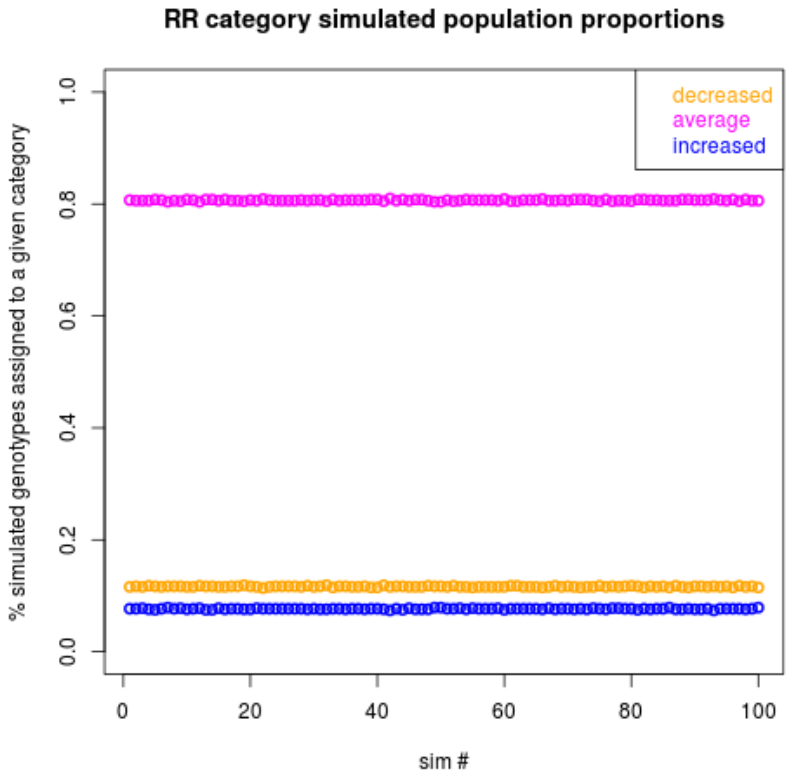

Figure 2.

References

Petersen GM, et al. A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22.1, 1q32.1 and 5p15.33. *Nat Genet.* 2010 Mar;42(3):224-8.

Wu C, et al. Genome-wide association study identifies five loci associated with susceptibility to pancreatic cancer in Chinese populations. *Nat Genet.* 2011 Dec 11;44(1):62-6.