Supplemental table 1. 22 independent SNPs associated with the risk of pancreatic cancer in genome-wide association studies

CHR	Loci	SNP	Position[a]	Reported gene	Minor/Major Allele	MAF[b]	MAF[c]	Reported OR (95% CI)	P-value	Risk allele[d]	Beta[e]	GWAS reference
1	1p36.33	rs13303010	894,573	NOC2L	G/A	0.13	0.11	1.26 (1.19-1.35)	8.4×10^{-14}	G	0.2311	Klein et al., 2018
1	1q32.1[1]	rs10919791	199,965,168	NR5A2	A/G	0.19	0.23	0.77 (0.71-0.84)	6.4×10^{-10}	G	0.2614	Peterson et al., 2010
1	1q32.1[2]	rs2816938	199,985,368	NR5A2	A/T	0.26	0.23	1.21 (1.17-1.26)	3.4×10^{-15}	A	0.1906	Zhang et al., 2016
2	2p14	rs1486134	67,639,769	ETAA1	G/T	0.30	0.28	1.14 (1.09–1.19)	3.4×10^{-9}	G	0.1310	Childs et al., 2015
3	3q28	rs9854771	189,508,471	TP63	A/G	0.34	0.36	0.89 (0.85-0.93)	2.4×10^{-8}	G	0.1165	Childs et al., 2015
5	5p15.33[1]	rs2736098	1,294,086	TERT	T/C	0.24	0.27	0.84 (0.79-0.88)	6.9×10^{-15}	C	0.1744	Wolpin et al., 2014
5	5p15.33[2]	rs31490	1,344,458	CLPTM1L	A/G	0.49[f]	0.45[f]	1.20 (1.14-1.27)	2.0×10^{-11}	A	0.1823	Wolpin et al., 2014
5	5p15.33[3]	rs35226131	1,295,373	TERT, CLPTM1L	T/C	0.02	0.03	0.67 (0.53-0.81)	2.2×10^{-8}	C	0.3425	Peterson et al., 2010
7	7p12	rs78417682	47,488,903	TNS3	C/G	0.10[g]	0.12[g]	0.85 (0.80-0.90)	1.4×10^{-7}	G	0.1863	Klein et al., 2018
7	7p14.1	rs17688601	40,866,663	SUGCT	A/C	0.25	0.27	0.88 (0.84-0.93)	1.1×10^{-8}	C	0.1278	Childs et al., 2015
7	7q32.3	rs6971499	130,680,521	LINC-PINT	C/T	0.13	0.15	0.81 (0.76-0.87)	7.4×10^{-14}	T	0.2107	Wolpin et al., 2014
8	8q21.11	rs2941471	76,470,404	HNF4G	G/A	0.41	0.43	0.89 (0.85-0.93)	6.6×10^{-10}	A	0.1165	Klein et al., 2018
8	8q24.21[1]	rs10094872	128,719,884	MYC	T/A	0.39	0.36	1.14 (1.10-1.19)	1.2×10^{-9}	T	0.1310	Zhang et al., 2016
8	8q24.21[2]	rs1561927	129,568,078	LINC00824, PVT1	C/T	0.25	0.27	0.89 (0.85-0.93)	7.1×10^{-8}	T	0.1165	Wolpin et al., 2014
9	9q34.1	rs687289	136,137,106	ABO	T/C	0.40[h]	0.35[h]	1.27 (1.20-1.35)	1.6×10^{-16}	A	0.2390	Amundadottir et al., 2009
13	13q12.2	rs9581943	28,493,997	PDX1	A/G	0.43	0.40	1.15 (1.12-1.19)	5.1×10^{-14}	A	0.1398	Wolpin et al., 2014
13	13q22.1	rs9543325	73,916,628	KLF5, KLF12	C/T	0.43	0.37	1.24 (1.19-1.28)	1.2×10^{-22}	C	0.2151	Peterson et al., 2010
16	16q23.1	rs7190458	75,263,661	BCAR1, CTRB1, CTRB2	A/G	0.06	0.04	1.36 (1.27-1.44)	1.3×10^{-11}	A	0.3075	Wolpin et al., 2014
17	17q12	rs4795218	36,078,510	HNF1B	A/G	0.21	0.23	0.88 (0.84-0.92)	1.3×10^{-8}	G	0.1278	Klein et al., 2018
17	17q24.3	rs11655237	70,400,166	LINC00673	T/C	0.14	0.12	1.26 (1.19–1.34)	1.4×10^{-14}	T	0.2311	Childs et al., 2015
18	18q21.32	rs1517037	56,878,274	GRP	T/C	0.17	0.19	0.86 (0.80-0.91)	3.3×10^{-8}	C	0.1508	Klein et al., 2018
22	22q12.1	rs16986825	29,300,306	ZNRF3	T/C	0.17	0.15	1.15 (1.10-1.20)	1.2×10^{-8}	T	0.1398	Wolpin et al., 2014

Abbreviations: CHR, chromosome; SNP, single nucleotide polymorphism; MAF, minor allele frequency; OR, odds ratio; CI, confidence interval; GWAS, genome-wide association study.

[a]SNP position and minor/major allele based on NCBI Human Genome Build 37

[b]Average of minor allele frequency among cases in PanScanI/II, PanScanIII, and PanC4

[c]Average of minor allele frequency among controls in PanScanI/II, PanScanIII, and PanC4

[d]Risk allele is the allele associated with increased risk of pancreatic cancer [if the risk allele is not our data, the complementary allele (e.g. A of rs687289) is reported.]

[e]Calculated beta coefficient per each risk allele using the reported OR in GWAS of PanScan, PanC4, or meta-analysis [if OR > 1 then beta = ln(OR); otherwise, beta = ln(1/OR)]

[f]Using rs401681 on 5p15.33 (T/C) reported in Klein, et al. 2018.

[g]Using rs73328514 on 7p12.3 (T/A) reported in Klein, et al. 2018

[h]Using rs505922 on 9q34 (C/T) reported in Klein, et al. 2018

Supplemental table 2. Missing data of 22 pancreatic cancer-associated SNPs by cohort

Loci	SNP	HPFS		NHS		PHS		WHI	
		Case	Control	Case	Control	Case	Control	Case	Control
1p36.33	rs13303010	2.4	34.9	7.5	38.9	33.3	78.5	21.7	68.8
1q32.1[2]	rs2816938	2.4	34.9	7.5	38.9	33.3	78.5	21.7	68.8
2p14	rs1486134	2.4	34.9	7.5	38.9	33.3	78.5	21.7	68.8
3q28	rs9854771	2.4	34.9	7.5	38.9	33.3	78.5	21.7	68.8
5p15.33[3]	rs35226131	2.4	34.9	7.5	38.9	33.3	78.5	21.7	68.8
7p12	rs78417682	2.4	34.9	7.5	38.9	33.3	78.5	21.7	68.8
7p14.1	rs17688601	2.4	34.9	7.5	38.9	33.3	78.5	21.7	68.8
8q21.11	rs2941471	2.4	34.9	7.5	38.9	33.3	78.5	21.7	68.8
8q24.21[1]	rs10094872	2.4	34.9	7.5	38.9	33.3	78.5	21.7	68.8
17q12	rs4795218	2.4	34.9	7.5	38.9	33.3	78.5	21.7	68.8
17q24.3	rs11655237	2.4	34.9	7.5	38.9	33.3	78.5	21.7	68.8
18q21.32	rs1517037	2.4	34.9	7.5	38.9	33.3	78.5	21.7	68.8
1q32.1[1]	rs10919791	12.0	76.9	31.3	79.5	40.0	78.5	21.7	68.8
5p15.33[1]	rs2736098	12.0	76.9	31.3	79.5	40.0	78.5	21.7	68.8
5p15.33[2]	rs31490	12.0	76.9	31.3	79.5	40.0	78.5	21.7	68.8
7q32.3	rs6971499	12.0	76.9	31.3	79.5	40.0	78.5	21.7	68.8
8q24.21[2]	rs1561927	12.0	76.9	31.3	79.5	40.0	78.5	21.7	68.8
9q34.1	rs687289	12.0	76.9	31.3	79.5	40.0	78.5	21.7	68.8
13q12.2	rs9581943	12.0	76.9	31.3	79.5	40.0	78.5	21.7	68.8
13q22.1	rs9543325	12.0	76.9	31.3	79.5	40.0	78.5	21.7	68.8
16q23.1	rs7190458	12.0	76.9	31.3	79.5	40.0	78.5	21.7	68.8
22q12.1	rs16986825	12.0	76.9	31.3	79.5	40.0	78.5	21.7	68.8

Note: The header "Missing percentage (%)" spans the HPFS, NHS, PHS, and WHI columns.

Abbreviations: HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; PHS, Physicans' Health Study; WHI, Women's Health Initiative; SNP, single nucleotide polymorphism; RAF, risk allelic frequency; uGRS, unweighted genetic risk score; wGRS, weighted genetic risk score.

Supplemental table 3. Descriptive characteristics of study subjects in HPFS, NHS, PHS, and WHI cohorts (Total N = 1,591)

Variables	HPFS Cases	HPFS Controls	NHS Cases	NHS Controls	PHS Cases	PHS Controls	WHI Cases	WHI Controls
	N=83	N=195	N = 147	N = 396	N = 90	N = 163	N = 180	N = 337
Matching factors								
Age								
Age at diagnosis (year), mean (SD)	73.1 (8.4)		73.0 (7.4)		73.2 (9.1)		72.3 (7.5)	
Age at blood draw (year), mean (SD)	65.5 (7.9)	65.4 (7.9)	60.5 (6.0)	60.6 (6.1)	57.3 (8.8)	55.0 (8.2)	67.3 (7.2)	67.2 (7.3)
Smoking								
Current smoker, %	9.6	11.8	18.5	16.7	17.8	17.2	7.3	5.4
Fasting status								
Fasting < 8 hours, %	41.0	40.0	30.6	23.2	70.0	73.6	0.0	0.0
Fasting >= 8 hours, %	59.0	60.0	69.4	76.8	30.0	26.4	100.0	100.0
Lifestyle and clinical factors								
Body mass index (kg/m^2), mean (SD)	25.7 (3.3)	25.7 (3.2)	26.1 (5.4)	25.3 (4.3)	25.6 (2.9)	24.7 (2.2)	27.2 (6.1)	26.8 (5.4)
Waist-to-hip ratio (inch/inch), mean (SD)	0.9 (0.1)	0.9 (0.1)	0.8 (0.1)	0.8 (0.1)	1.0 (0.1)	0.9 (0.1)	0.8 (0.1)	0.8 (0.1)
Physical activity (MET-hr/wk), mean (SD)	50.6 (65.1)	41.0 (44.0)	16.6 (19.1)	16.8 (18.6)	12.1 (11.1)	14.4 (12.5)	12.9 (12.8)	15.6 (16.0)
Diagnosed diabetes (yes), %	4.8	3.6	6.1	3.5	4.4	1.2	6.7	3.0
Biomarkers								
Proinsulin (pM), mean (SD)	21.8 (24.9)	19.6 (34.0)	15.4 (15.3)	11.6 (16.4)	24.3 (29.0)	14.8 (11.4)	11.6 (10.2)	10.0 (9.2)
Adiponectin (ug/mL), mean (SD)	5.0 (2.3)	6.1 (3.8)	8.9 (6.1)	8.5 (4.8)	5.4 (3.1)	5.8 (2.8)	9.3 (5.7)	10.0 (5.7)
Interleukin-6 (pg/mL), mean (SD)	1.8 (2.9)	1.6 (2.2)	2.7 (5.1)	1.6 (3.1)	2.0 (3.8)	2.3 (4.6)	2.6 (4.2)	2.4 (3.5)
Total BCAAs (µM), mean (SD)	481.2 (85.9)	387.9 (195.1)	393.6 (201.6)	279.5 (233.1)	467.6 (234.4)	413.6 (228.7)	417.6 (115.9)	409.5 (87.2)
Valine (µM), mean (SD)	223.8 (35.0)	219.6 (44.4)	227.2 (46.5)	220.8 (36.9)	258.1 (45.8)	238.5 (41.5)	210.0 (45.8)	203.8 (40.3)
Leucine (µM), mean (SD)	167.2 (33.9)	159.3 (37.5)	161.1 (37.6)	155.2 (28.2)	195.4 (43.0)	182.4 (40.6)	139.9 (34.4)	134.2 (29.7)
Isoleucine (µM), mean (SD)	90.2 (21.3)	85.2 (23.0)	85.9 (22.3)	83.3 (20.3)	107.6 (28.8)	97.7 (25.3)	77.2 (21.3)	72.7 (18.0)
Genetic risk factors								
22 SNPs (RAF[a]), %								
1p36.33 – rs13303010_G	16.0	21.2	18.5	19.6	13.9	17.0	15.4	19.0
1q32.1 – rs10919791_G	85.5	79.0	78.9	77.5	86.1	79.8	83.1	77.4
1q32.1 - rs2816938_A	24.7	24.4	17.4	24.7	21.7	24.4	26.9	19.2
2p14 - rs1486134_G	29.5	26.9	27.2	29.4	27.8	29.4	29.4	28.8
3q28 - rs9854771_G	69.9	64.3	63.6	65.1	63.3	58.9	67.5	63.2
5p15.33[1] – rs2736098_C	77.9	72.7	79.4	73.9	79.8	72.6	77.1	74.2
5p15.33[2] – rs31490_A	41.5	40.3	51.7	37.7	50.6	37.8	48.0	39.1
5p15.33[3] - rs35226131_C	99.1	98.1	97.1	97.3	97.2	96.4	97.2	96.6
7p12 - rs78417682_G	89.4	89.2	88.1	91.0	90.5	91.5	91.4	92.1
7p14.1 - rs17688601_C	77.7	72.1	74.4	72.8	76.7	76.2	78.9	73.8
7q32.3 – rs6971499_T	86.7	87.2	86.4	83.7	83.5	87.2	83.3	83.8
8q21.11 – rs2941471_A	55.9	57.8	61.9	58.3	61.4	57.5	58.0	62.2
8q24.21[1] - rs10094872_T	33.9	40.7	37.9	35.6	39.9	33.8	39.2	35.3
8q24.21[2] - rs1561927_T	75.3	72.6	74.8	72.6	74.4	73.3	68.9	75.2
9q34.1 – rs687289_A	40.2	34.1	36.6	36.5	36.3	29.0	38.9	33.4

Variables	HPFS		NHS		PHS		WHI	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
	N=83	N=195	N = 147	N = 396	N = 90	N = 163	N = 180	N = 337
13q12.2 – rs9581943_A	50.3	36.9	46.3	38.6	35.2	42.6	41.2	40.3
13q22.1 – rs9543325_C	44.0	42.1	41.8	36.7	47.8	35.9	40.6	36.5
16q23.1 – rs7190458_A	2.9	4.3	7.7	4.0	5.9	5.4	3.9	2.8
17q12 - rs4795218_G	77.7	75.5	79.3	78.7	73.1	79.7	80.3	72.8
17q24.3 - rs11655237_T	9.6	11.5	9.6	13.1	12.3	11.6	14.2	12.0
18q21.32 - rs1517037_C	78.9	82.8	88.1	83.6	86.7	81.7	84.4	85.3
22q12.1 – rs16986825_T	16.3	15.9	15.3	14.7	14.4	15.6	16.6	15.5
uGRS, mean (SD)	23.7 (2.8)	23.0 (2.6)	23.6 (2.6)	22.9 (2.6)	23.6 (3.0)	22.7 (2.6)	23.7 (2.8)	22.8 (2.7)
wGRS[b], mean (SD)	0.2 (1.0)	-0.1 (1.0)	0.2 (1.0)	-0.1 (1.0)	0.2 (1.0)	-0.1 (1.0)	0.2 (1.0)	-0.1 (1.0)

Abbreviations: HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; PHS, Physicans' Health Study; WHI, Women's Health Initiative; MET, metabolic equivalent of task; BCAAs, branched-chain amino acids; SNP, single nucleotide polymorphism; RAF, risk allelic frequency; uGRS, unweighted genetic risk score; wGRS, weighted genetic risk score; SD, standard deviation.

[a]Estimated risk allelic frequency based on raw genotype dosage data [RAF = (average of allelic dosage)/2]

[b]Standardized variables with mean = 0 and SD= 1 within each cohort

[c]Complete missing Variables

Supplemental table 4. Univariable odds ratios and 95% CIs with pancreatic cancer risk by cohort[a]

Variables	Pooled data (N = 1,591) OR (95% CI)	HPFS (N = 278) OR (95% CI)	NHS (N = 543) OR (95% CI)	PHS (N = 253) OR (95% CI)	WHI (N = 517) OR (95% CI)
Lifestyle and clinical factors					
Body mass index[b]	1.15 (1.03, 1.27)	0.99 (0.76, 1.28)	1.17 (0.98, 1.40)	1.51 (1.13, 2.00)	1.07 (0.90, 1.29)
Waist-to-hip ratio[b]	1.19 (1.06, 1.33)	1.17 (0.87, 1.57)	1.25 (0.98, 1.60)	1.34 (0.95, 1.88)	1.13 (0.94, 1.35)
Physical activity[b]	0.94 (0.85, 1.05)	1.19 (0.93, 1.51)	1.01 (0.84, 1.21)	0.84 (0.65, 1.08)	0.82 (0.67, 1.00)
Diagnosed diabetes (yes)	2.36 (1.32, 4.21)	1.34 (0.38, 4.78)	2.68 (0.82, 8.75)	3.61 (0.66, 19.74)	2.60 (1.05, 6.41)
Circulating biomarkers					
Proinsulin[b]	1.24 (1.10, 1.40)	1.06 (0.81, 1.39)	1.33 (1.01, 1.74)	2.39 (1.22, 4.69)	1.19 (1.00, 1.42)
Adiponectin (≥ 4.4 ug/ml)	0.57 (0.43, 0.76)	0.52 (0.29, 0.92)	0.64 (0.35, 1.14)	0.54 (0.29, 1.01)	0.58 (0.34, 0.99)
Interleukin-6[b]	1.10 (0.98, 1.22)	1.03 (0.80, 1.33)	1.30 (1.01, 1.66)	0.93 (0.66, 1.29)	1.07 (0.90, 1.27)
Total BCAAs[b]	1.37 (1.14, 1.64)	1.38 (0.86, 2.23)	1.74 (0.92, 3.29)	2.59 (1.29, 5.21)	1.24 (1.00, 1.53)
Genetic risk score					
wGRS[b]	1.37 (1.23, 1.53)	1.29 (0.97, 1.70)	1.32 (1.08, 1.61)	1.42 (1.08, 1.87)	1.43 (1.19, 1.72)

Abbreviations: HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; PHS, Physicans' Health Study; WHI, Women's Health Initiative; OR, odds ratio; CI, confidence interval; BCAAs, branched-chain amino acids; wGRS, weighted genetic risk score.

[a]Estimated based on raw data only

[b]Standardized variables within each cohort with mean = 0 and SD= 1 within each cohort

Supplemental table 5. Estimated ORs and 95% CIs from multivariable[a] risk models for pancreatic cancer including clinical/biomarker model

	Clinical model	Clinical/ genetic model	Clinical/ biomarker model	Clinical/ genetic/ biomarker model
Full follow-up period				
Model comparison (*P*-value[b])		3.24e-08	2.10e-05	6.03e-05
Model AUC	0.61	0.65	0.64	0.67
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Body mass index[c]	1.08 (0.97, 1.21)	1.07 (0.95, 1.20)	0.99 (0.88, 1.11)	0.98 (0.86, 1.10)
Waist-to-hip ratio[c]	1.13 (1.01, 1.26)	1.12 (1.00, 1.26)	1.08 (0.96, 1.22)	1.08 (0.96, 1.21)
Physical activity[c]	0.96 (0.86, 1.06)	0.95 (0.85, 1.06)	0.97 (0.87, 1.08)	0.97 (0.86, 1.08)
Diagnosed diabetes (yes)	2.10 (1.16, 3.79)	2.19 (1.19, 4.02)	1.63 (0.89, 3.01)	1.70 (0.91, 3.19)
wGRS[c]		1.37 (1.22, 1.53)		1.36 (1.21, 1.52)
Proinsulin[c]			1.16 (1.02, 1.30)	1.16 (1.03, 1.31)
Adiponectin (≥ 4.4 ug/ml)			0.73 (0.56, 0.95)	0.76 (0.58, 0.99)
Interleukin-6[c]			1.09 (0.99, 1.21)	1.10 (0.99, 1.23)
Total BCAAs[c]			1.27 (1.05, 1.53)	1.25 (1.04, 1.51)
0-10 years follow-up period				
Model comparison (*P*-value[b])		2.91e-07	1.05e-03	2.92e-03
Model AUC	0.61	0.67	0.65	0.69
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Body mass index[c]	1.05 (0.91, 1.22)	1.04 (0.90, 1.21)	0.97 (0.83, 1.13)	0.96 (0.82, 1.12)
Waist-to-hip ratio[c]	1.08 (0.93, 1.25)	1.06 (0.91, 1.23)	1.02 (0.88, 1.19)	1.00 (0.86, 1.17)
Physical activity[c]	0.86 (0.74, 1.00)	0.86 (0.74, 1.01)	0.87 (0.74, 1.02)	0.88 (0.75, 1.03)
Diagnosed diabetes (yes)	2.22 (1.09, 4.54)	2.14 (1.02, 4.50)	1.71 (0.81, 3.59)	1.65 (0.77, 3.56)
wGRS[c]		1.44 (1.25, 1.67)		1.43 (1.23, 1.65)
Proinsulin[c]			1.08 (0.94, 1.25)	1.10 (0.94, 1.27)
Adiponectin (≥ 4.4 ug/ml)			0.67 (0.47, 0.97)	0.70 (0.48, 1.02)
Interleukin-6[c]			1.12 (0.98, 1.28)	1.13 (0.98, 1.30)
Total BCAAs[c]			1.28 (1.04, 1.58)	1.24 (1.00, 1.54)

Abbreviations: AUC, Area under the ROC curve; OR, odds ratio; CI, confidence interval; BCAAs, branched-chain amino acids; wGRS, weighted genetic risk score.

[a]Adjusted for matching factors, age, cohort (also gender), race/ethnicity, smoking status, fasting status, and month/year of blood collection.

[b]*P*-value was estimated from the likelihood ratio test comparing the clinical/genetic model to the clinical model, clinical/biomarker model to the clinical model, and the clinical/genetic/biomarker model to the clinical/genetic model.

[c]Standardized variables with mean = 0 and SD= 1 within each cohort

Supplemental figure 1. Flow diagram of study participants and missing data

278 HPFS (83 cases, 195 controls)	543 NHS (147 cases, 396 controls)	253 PHS (90 cases, 163 controls)	517 WHI (180 cases, 337 controls)

| **No. of samples with missing data**

[Survey data]
0 BMI
48 WHR
0 MET-score
0 Diabetes

[Blood sample data]
31 Proinsulin
33 Adiponectin
32 Interleukin-6
32 Total BCAAs
70 22 SNPs | **No. of samples with missing data**

[Survey data]
0 BMI
143 WHR
0 MET-score
0 Diabetes

[Blood sample data]
173 Proinsulin
153 Adiponectin
174 Interleukin-6
180 Total BCAAs
165 22 SNPs | **No. of samples with missing data**

[Survey data]
0 BMI
59 WHR
0 MET-score
0 Diabetes

[Blood sample data]
114 Proinsulin
71 Adiponectin
70 Interleukin-6
48 Total BCAAs
158 22 SNPs | **No. of samples with missing data**

[Survey data]
9 BMI
2 WHR
0 MET-score
0 Diabetes

[Blood sample data]
4 Proinsulin
0 Adiponectin
0 Interleukin-6
5 Total BCAAs
271 22 SNPs |

1,591 total subjects (500 cases, 1,091 controls)