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Case Control Study

Single-nucleotide polymorphisms based genetic risk score in the prediction of pancreatic cancer risk

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Abstract**BACKGROUND**

Disease-related single nucleotide polymorphisms (SNPs) based genetic risk score (GRS) has been proven to provide independent inherited risk other than family history in multiple cancer types.

AIM

To evaluate the potential of GRS in the prediction of pancreatic cancer risk.

METHODS

In this case-control study (254 cases and 1200 controls), we aimed to evaluate the association between GRS and pancreatic ductal adenocarcinoma (PDAC) risk in the Chinese population. The GRS was calculated based on the genotype information of 18 PDAC-related SNPs for each study subject (personal genotyping information of the SNPs) and was weighted by external odd ratios (ORs).

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RESULTS

GRS was significantly different in cases and controls (1.96 ± 3.84 in PDACs vs 1.09 ± 0.94 in controls, $P < 0.0001$). Logistic regression revealed GRS to be associated with PDAC risk [OR = 1.23, 95% confidence interval (CI): 1.13-1.34, $P < 0.0001$]. GRS remained significantly associated with PDAC (OR = 1.36, 95%CI: 1.06-1.74, $P = 0.015$) after adjusting for age and sex. Further analysis revealed an association of increased risk for PDAC with higher GRS. Compared with low GRS (< 1.0), subjects with high GRS (2.0) were 99% more likely to have PDAC (OR: 1.99, 95%CI: 1.30-3.04, $P = 0.002$). Participants with intermediate GRS (1.0-1.9) were 39% more likely to have PDAC (OR: 1.39, 95%CI: 1.03-1.84, $P = 0.031$). A positive trend was observed (P trend = 0.0006).

CONCLUSION

GRS based on PDAC-associated SNPs could provide independent information on PDAC risk and may be used to predict a high risk PDAC population.

Key words: Pancreatic cancer; Single nucleotide polymorphisms; Genetic risk score; Chinese population; Genome-wide association study

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Core tip: Pancreatic ductal adenocarcinoma (PDAC) is a highly malignant tumor with no effective method for early diagnosis and high-risk population screening. In this pioneer study, we evaluated single nucleotide polymorphisms based genetic risk score (GRS) in the prediction of PDAC risk. Our results revealed that GRS was significantly associated with PDAC. Compared with low GRS (< 1.0), subjects with high GRS (2.0) were 99% more likely to be PDAC. Although further verification is needed, our study suggested that GRS was an independent risk factor for PDAC.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies worldwide. With an estimated death toll of 330400 in 2012, it is the seventh leading cause of cancer death in both sexes^[1]. In China, PDAC ranks among the top ten most common cancers. The estimated new cases and death toll in 2015 was 90100 and 79400, respectively^[2,3]. In addition, data showed that PDAC mortalities have increased rapidly in China during the past decades. There were 27482 deaths in 1990, while the number increased to 59423 in 2013^[4]. Therefore, PDAC has become a major public health issue both in China and worldwide.

As one of the most lethal cancers, early diagnosis of PDAC is essential to effective treatment and better prognosis. Unfortunately, due to the lack of symptoms at an early stage and no efficient way of screening, early diagnosis of PDAC remains challenging^[5]. Carbohydrate antigen 19-9 and carcinoembryonic antigen are commonly used biomarkers. However, carbohydrate antigen 19-9 and carcinoembryonic antigen are not PDAC specific, and a small group of patients do not show an elevated level of these two biomarkers^[6,7]. Computed tomography or other imaging technologies may increase diagnostic utilities for PDAC, but no evidence shows their benefits in screening. It will be less cost-effective to screen the entire population. A model to select a high-risk population group for screening would be of great clinical utilization and public health importance. Known risk factors for PDAC includes diabetes^[8], smoking^[9] and family history.

About 5%-10% of PDAC cases are familial pancreatic cancer, defined as the patient having two first degree relatives diagnosed with pancreatic cancer^[10]. Those patients are usually linked with germline mutation (BRCA1, BRCA2)^[11] or cancer syndrome (Lynch syndrome)^[12]. However, with a trend of decreased family sizes^[13], family

history could be uninformative, especially in China where the “one-child policy” had been applied in the past decades. Disease-related single nucleotide polymorphisms (SNPs) based genetic risk score (GRS) could be a promising substitute. It has been proven to provide independent inherited risk information other than family history in multiple cancer types and can be associated with early onset of diseases^[14-17]. PDAC risk associated SNPs were revealed by genome-wide association studies (GWAS)^[18-22]. The application of these results needs further investigation. Therefore, we conducted the first study to evaluate the association between GRS and PDAC in the Chinese population.

MATERIALS AND METHODS

Study population and genotyping

This study included 254 pathologically confirmed PDAC patients of Chinese Han population from the Department of Pancreatic Surgery in Huashan Hospital diagnosed between March 2013 and August 2014. They had been recruited for a PDAC-associated SNP verification study^[23]. The control population was a healthy community population from east China^[24]. Written informed consent was obtained from each participant. Data was de-identified after collection. Genotype and phenotype information was retrospectively collected from the previous studies. This study was approved by the Institutional Review Board of Huashan Hospital affiliated to Fudan University.

Genotype data of 21 SNPs was obtained from our previous SNP evaluation study. These SNPs were reported to be associated with PDAC risk by GWAS or pathway study^[18-22,25]. SNPs were genotyped by a Sequenom MassARRAY iPLEX system (Sequenome Inc., San Diego, CA, United States) and Taqman PCR (rs4885093 and rs10919791)^[23]. GWAS was performed by Illumina Human OmniExpress Bead Chips^[24] on the control samples. Imputation was performed using IMPUTE 2.2.2 program based on 1000 Genomes Project CHB+JPT population data (Phase I version 3, release March 2012) if the SNPs were not included in the GWAS chip.

GRS calculation and statistical analysis

A GRS was calculated for each subject based on personal genotype of the SNPs and was weighted by external odd ratios (ORs from previous GWAS studies): Carrying two risk alleles = $1 * OR^2$; carrying one risk allele = $1 * OR$; and not carrying risk allele = 1. The final GRS was also adjusted by minor allele frequency. A detailed method of GRS calculation was described in the previous study^[17]. The OR used for calculations were from previous GWAS studies. In this study, 18 out of 21 SNPs were used in the final calculation of GRS. rs2736098 did not pass quality control. rs12413624 and rs792864 showed different minor allele between case and control group, possibly due to the difference between positive and negative chains of DNA during genotyping (the cases and controls were genotyped separately with different platforms). This was not a problem for OR calculations in the previous study. But for GRS calculation, we just ruled out these two SNPs for caution. Information of all 21 SNPs was displayed in Table 1.

The *t*-test was used to evaluate the differences of mean GRS mean between cases and controls. GRS data first underwent log transformation to achieve normality for the *t*-test. After the log transformation, GRS of both groups are normally distributed (Supplementary Figure 1). GRS were not log transformed for other analysis. A univariate and a multivariate mode controlled for age and sex were used to evaluate the association between GRS and PDAC risk. Chi-square trend tests and receiver operating characteristic curve was used to evaluate the performance of GRS in predicting PDAC risk. All statistical analyses were performed using SAS 9.3, and two-tailed $P < 0.05$ were considered as significant.

The statistical methods of this study were reviewed by Wang R from Yale School of Public Health, Department of Chronic Disease Epidemiology.

RESULTS

Table 2 shows the basic characteristics of the study population. The control group was significantly younger (case *vs* control: 63.31 ± 10.01 *vs* 48.80 ± 15.49 , $P < 0.01$). All tested SNPs were polymorphic in the Chinese population. The prevalence of minor allele of SNPs in the Chinese 1000 genome project and the PDAC patients of our study were presented in our previous study^[23]. The mean GRS for PDAC patients was 1.96 ± 3.84 , and the mean for controls was 1.09 ± 0.94 . The GRS for the two groups were

Table 1 Information of single nucleotide polymorphisms for calculating genetic risk score

Chromosome	SNP	Region	Related-gene	Previous GWAS study			
				OP ¹	RA	OR	RAF
1	rs10919791	1q32.1	<i>NR5A2</i>	EU	A	0.77	0.19
5	rs2736098	5p15.33	<i>TERT, CLPTMIL</i>	EU	T	0.8	NA ¹
5	rs401681	5p15.33	<i>CLPTMIL</i>	EU	T	1.19	0.49
5	rs2255280	5p13.1	<i>DAB2</i>	CH	G	0.81	0.32
6	rs2317900	6p25.3	<i>FOXQ1</i>	JA	C	1.288	0.41
7	rs6971499	7q32.3	<i>LINC-PINT</i>	EU	C	0.79	NA ¹
7	rs7779540	7q36.2	<i>DPP6</i>	JA	A	3.69	0.17
7	rs167020	7q36.3	<i>SHH</i>	EU	A	1.17	0.3
8	rs1561927	8q24.21	<i>MIR1208, PVT1</i>	EU	C	0.87	NA ¹
9	rs2073828	9q34.2	<i>ABO</i>	EU	A	0.85	0.37
9	rs505922	9q34.2	<i>ABO</i>	EU	C	1.2	0.35
10	rs12413624	10q26.11	<i>PRLHR</i>	CH	T	1.23	0.42
12	rs792864	12p11.21	<i>BICD1</i>	JA	A	0.71	0.24
13	rs9581943	13q12.2	<i>PDX1</i>	EU	A	1.46	NA ¹
13	rs4885093	13q22.1	NA	CH	C	1.25	0.5
13	rs9543325	13q22.1	NA	EU	C	1.26	0.37
16	rs7190458	16q23.1	<i>BCAR1, CTRB1, CTRB2</i>	EU	A	1.46	NA ¹
21	rs372883	21q21.3	<i>BACH1</i>	CH	C	0.79	0.39
21	rs1547374	21q22.3	<i>TFF1</i>	CH	G	0.79	0.4
22	rs16986825	22q12.1	<i>ZNRF3</i>	EU	T	1.18	NA ¹
22	rs5768709	22q13.32	<i>FAM19A5</i>	CH	G	1.25	0.28

¹Not available. These loci were not included in the final calculation of genetic risk score. OP: Original genome-wide association study population; RA: Risk allele; OR: Odds ratio from genome-wide association studies; RAF: Risk allele frequency in our study; EU: European; JA: Japanese; CH: Chinese; GWAS: Genome-wide association studies.

significantly different ($P < 0.0001$). Further univariate logistic regression mode revealed that GRS was positively associated with PDAC risk [Table 3, OR = 1.23, 95% confidence interval (CI): 1.13-1.34, $P < 0.0001$]. Because the control group was significantly younger, a multivariate model was also conducted with age and sex as covariates. The GRS remained positively associated with PDAC (Table 3, OR = 1.36, 95% CI: 1.06-1.74, $P = 0.015$).

We further analyzed the risk of PDAC in different GRS groups among the study population. Compared to those with low GRS (< 1), participants with intermediate GRS (1-2) were 39% more likely to have PDAC (OR: 1.39, 95% CI: 1.03-1.84, $P = 0.031$). Those with high GRS were nearly two times more likely to have PDAC (OR: 1.99, 95% CI: 1.30-3.04, $P = 0.002$). A positive trend was also observed (P trend = 0.0006, Figure 1A). Figure 1B showed the increased risks of PDAC in patients with increased GRS by different percentiles (P trend = 0.0008). Patients with GRS $\geq 90^{\text{th}}$ percentile would have a 2.29-fold increased risk for PDAC (95% CI: 1.25-4.21, $P = 0.007$). The receiver operating characteristic curve analysis showed that the area under the receiver operating characteristic curve (AUC) was 0.5675 for predicting PDAC risk (Supplementary Figure 2). A positive trend was also observed in the multivariate model, which adjusted for age and sex. The percentage of PDAC cases with low (< 1.0), intermediate (1.0-1.9) and high (≥ 2.0) GRS were 14.49%, 19.57% and 25.90%, respectively (Figure 2). Patients with GRS $\geq 90^{\text{th}}$ percentile showed a 1.84-fold increased risk for pancreatic cancer in the multivariate mode (Figure 3).

DISCUSSION

To our best knowledge, this was the first study to evaluate the performance of SNPs based GRS for predicting PDAC risk in the Chinese population. In this case-control study, we found that: (1) GRS was an independent predictor of PDAC; and (2) As reflecting inherited risks, patients with higher GRS would have higher risks of PDAC

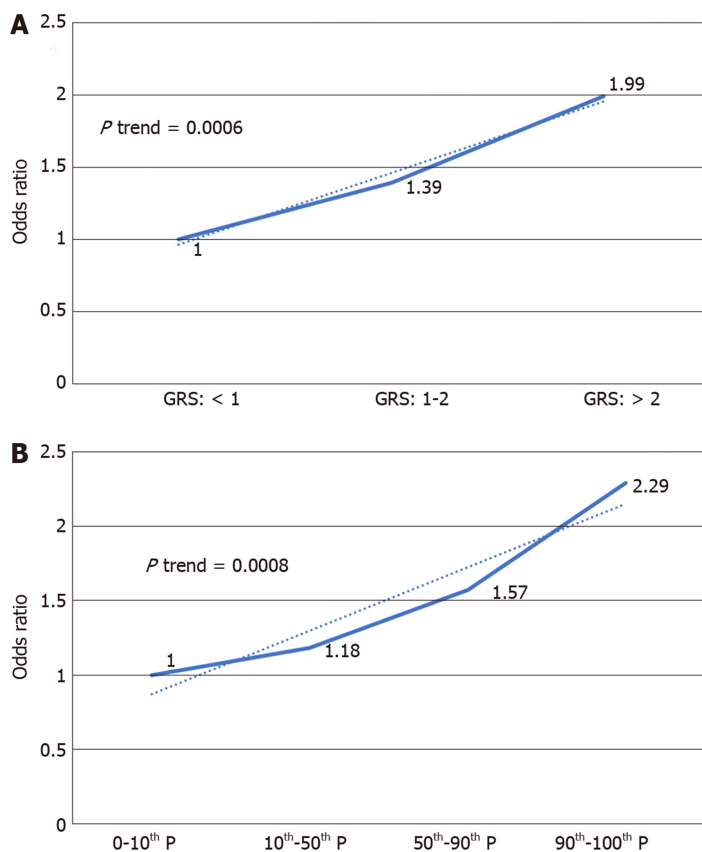


Figure 1 Increased risk of pancreatic ductal adenocarcinoma with increased genetic risk score in a univariate model. A: 1, 2 being genetic risk score cut-off value; B: Percentile as cut-off value. GRS: Genetic risk score.

in the study population.

Chronic disease such as heart disease and cancer have a complex etiology. Genetic factors and lifestyle factors both contribute to the development of these chronic diseases^[26,27]. With the surge of GWAS, common germ line variations have been studied for their association with heart disease and many cancers. GRS is a disease risk prediction system based on disease risk related SNPs. It has been applied in the prediction of heart disease^[28,29], obesity^[30], prostate cancer^[15,16,31] and colorectal cancer (CRC)^[32,33].

Ripatti *et al*^[28] and Thanassoulis *et al*^[29] both reported GRS to be an independent risk factor for cardiovascular disease. However, GRS did not improve the risk stratification system with traditional risk factors and family history in their studies. Belsky *et al*^[30] reported GRS to be a statistically significant predictor of body mass index and obesity in the white population of the Atherosclerosis Risk in Communities cohort (AUC: 0.57, 95%CI: 0.55-0.58)^[30].

In CRC, Weigl *et al*^[33] reported GRS, independent of family history, was associated with CRC risk (OR = 3.00, 95%CI: 2.24-4.02, highest *vs* lowest decile). More importantly, their study revealed that patients with both GRS in the highest decile and a family history had a 6-fold increased risk for CRC compared those who with no family history and a GRS in the lowest decile. Similar results were also reported by Jo *et al*^[32]. Individuals with a family history of CRC in the highest quartile of GRS when compared to subjects without a family history of CRC in the lowest quartile of GRS had a significantly increased risk for CRC [OR: 47.9, 95%CI: 4.9-471.8 (men); OR: 22.3, 95%CI: 1.4-344.2 (women)].

In prostate cancer, researchers focused on the implementation of GRS to reduce unnecessary biopsies. Aly *et al*^[15] reported the use of GRS could avoid 480 biopsies (22.7%) at a cost of missing a prostate cancer diagnosis in 3% of patients characterized as having an aggressive disease. Kader *et al*^[31] reported adding the genetic score to the best clinical model improved the AUC from 0.62 to 0.66 (*P* < 0.001). Sun *et al*^[16] compared the family history and GRS in five different populations and found that the AUC of GRS for predicting positive prostate cancer biopsy was significantly higher (0.58-0.62) than family history (0.51-0.55) in each study population (*P* < 0.05).

For PDAC, previous studies suggested genetic inheritance contributes to the risk of

Table 2 Characteristics of study population

Variables	Case, n = 254		Control, n = 1200		P value
	n	%	n	%	
Sex					
Male	156	64.42	748	62.23	0.83 ¹
Female	98	38.58	452	37.67	
Age at diagnosis, mean ± SD	63.31	10.01	48.80	15.49	0.0001 ²
GRS, mean ± SD	1.96	3.84	1.09	0.94	< 0.0001 ³
GRS: < 1	127	50.00	723	60.25	0.002 ¹
GRS: 1-2	91	35.83	374	31.17	
GRS: > 2	36	14.17	103	8.58	
< 10 th P	19	7.48	127	10.58	0.007 ¹
10 th -50 th P	87	34.25	494	41.17	
50 th -90 th P	111	43.70	471	39.25	
90 th P	37	14.57	108	9.00	

¹Chi-square.²t-test.³Genetic risk score log transformed for t-test. GRS: Genetic risk score.

developing PDAC. Lochan *et al.*^[34] reported that individuals with first degree relatives of any malignancy would have 1.98-fold increased risk of PDAC. In another study, individuals with positive family history of pancreatic cancer were reported to have a 2.2-fold increased risk compared to those with negative family history^[35]. Mucci *et al.*^[36] reported that when one twin had PDAC, the risks of PDAC increased by 4.3-fold for monozygotic twin and 3.7-fold for dizygotic twins. However, familial pancreatic carcinoma only counts for 5%-10% of total cases. Furthermore, family history may be influenced by family size, age and survival status of male relatives, recall ability and prevalence of the disease in populations^[16]. The overall family history reported rate was only 64.3% for cases and 62.5% for controls in the PanScan Consortium^[37].

Various loci related to PDAC risk from different populations were reported^[18-22]. However, the practical value of those loci from GWAS has not been fully studied. In this study, we explored the potential association between GRS and PDAC risk to find a novel method to define a pancreatic cancer high risk group. As mentioned above, there is no effective screening method for pancreatic cancer, and the downsize of households often leaves family history uninformative. Similar to previous studies in prostate cancer and CRC^[15,16,31-33], we found an association between GRS and PDAC (OR = 1.36). More importantly, an increasing trend was observed. Higher GRS was associated with a higher risk of PDAC in our study population. The only other study that constructed a PDAC risk prediction model using SNPs was reported by Klein *et al.*^[37]. Three SNPs from PanScan population based GWAS (rs9543325, rs401681, rs3790844) were included in the model^[22]. Other nongenetic factors included in the model were smoking, diabetes, alcohol consumption, ABO blood type, body mass index and family history. In Klein *et al.*^[37], the AUC of the risk model with only SNPs was 0.57, while the number was 0.58 for risk model with only nongenetic factors. A model with both genetic and nongenetic factors had a significantly larger AUC (0.61) than any other model ($P < 0.0001$). Due to the retrospective design of our study, we were not able to collect nongenetic risk factor from de-identified data. We included all loci from precious GWAS to construct a model with 18 SNPs. The AUC of our SNPs model (0.57) was close to the PanScan study. This may indicate that some common variation is shared by populations with different ancestors, and GRS could provide independent information on PDAC risk in the Chinese population. Although the result may need further confirmation, our study showed the potential of GRS in a PDAC high risk population selection. GRS could be applied in selecting high risk individuals for further tests, such as computed tomography or endoscopic ultrasound.

Several limitations should be noticed. First, this is a retrospective case-control study with a relatively small sample size of PDAC patients. The results of the study should be validated in a larger cohort before being applied in clinical use. Second, we were unable to evaluate the relationship of family history and GRS due to the uninformative family history in this Chinese population and the nature of our study design. However, based on the reported studies of other cancers, we believed that GRS could provide independent inherited risks supplementary to family history.

Table 3 Univariate/multivariate logistic regression results

Univariate logistic regression	OR (95%CI)	P value
GRS	1.23 (1.13-1.34)	< 0.0001
Multivariate logistic regression	OR (95%CI)	P value
GRS	1.36 (1.06-1.74)	0.015
Age at diagnosis/enrollment	1.14 (1.12-1.17)	< 0.0001
Sex	0.84 (0.61-1.16)	0.28
Subgroup analysis¹	OR (95%CI)	P value
GRS: < 1 (Ref) ²	-	-
GRS: 1-2	1.39 (1.03-1.84)	0.031
GRS: > 2	1.99 (1.30-3.04)	0.002
< 10 th P (Ref) ³	-	-
10 th -50 th P	1.18 (0.69-2.01)	0.548
50 th -90 th P	1.57 (0.93-2.66)	0.089
> 90 th P	2.29 (1.25-4.21)	0.007

¹Univariate mode.²P trend = 0.0006.³P trend = 0.0008. OR: Odds ratio; CI: Confidence interval; GRS: Genetic risk score.

Third, the cutoff values of GRS in the trend analysis (*e.g.*, GRS = 1 or 2; 10th percentile, 50th percentile, 90th percentile) were chosen based on the frequency distribution of GRS. The GRS was normally distributed after log transformation. However, from the aspect of application, it is better to choose the cut-off value on the original GRS. Due to the relatively small sample size, our GRS frequency distribution may not represent the true distribution, and one may argue our cutoff values to be relatively subjective. This should not discourage the use of GRS because population average risks were considered when calculating GRS (carrying two risk alleles = 1 * OR², carrying one risk allele = 1 * OR, not carrying risk allele = 1). GRS over one would indicate an increased inherited risk while GRS less than one would indicate a decreased inherited risk. In fact, population average level of GRS would always be slightly over one. The definition of controls is population with the potential to become cases. The GRS of our control group was 1.09 ± 0.94. The result fits the epidemiology principle and may indicate that a small number of individuals had increased inherited risks, but the disease had not occurred at the time of enrollment.

In conclusion, PDAC-associated SNPs based GRS could provide information on PDAC risk. This finding might be applied in clinical use for personal screening of PDAC after a validation in a larger cohort.

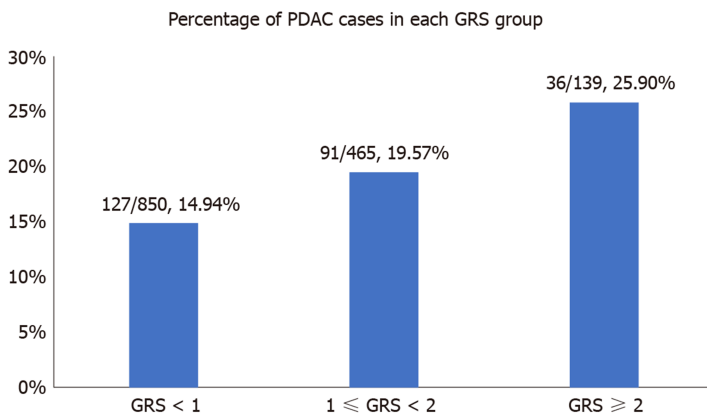


Figure 2 Percentage of pancreatic ductal adenocarcinoma cases in different genetic risk score groups. PDAC: Pancreatic ductal adenocarcinoma; GRS: Genetic risk score.

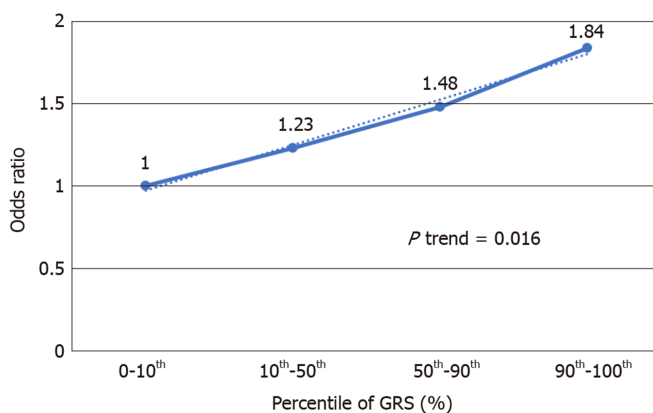


Figure 3 Increased risk of pancreatic ductal adenocarcinoma with increased genetic risk score in multivariate model adjusted for age and sex. GRS: Genetic risk score.

ARTICLE HIGHLIGHTS

Research background

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies worldwide. Lacking effective methods for screening, the early diagnosis of PDAC remains challenging leading to an extremely poor prognosis of PDAC.

Research motivation

Single nucleotide polymorphisms based genetic risk score (GRS) has been proven to provide independent inherited risk information in other cancers. GRS may be a promising way to select a high risk PDAC population for further screening.

Research objectives

We constructed a GRS based on 18 PDAC related single nucleotide polymorphisms, and we evaluated the effectiveness of GRS in the prediction of PDAC risk.

Research methods

We used personal genotyping data to calculate individual GRS. GRS was also weighted by population odds ratio. Final GRS was evaluated for the prediction of PDAC risk in the general Chinese population.

Research results

GRS was significantly associated with PDAC risk after being adjusted for age and sex (odds ratio = 1.36, 95% confidence interval: 1.06-1.74, *P* = 0.015). Higher GRS indicated a higher risk for PDAC (odds ratio = 2.29, 95% confidence interval: 1.25-4.21, *P* = 0.007, highest decile *vs* lowest decile). The area under the curve for GRS for PDAC risk was 0.5675.

Research conclusions

GRS was an independent predictor of PDAC. As reflecting inherited risks, patients with higher GRS would have higher risks of PDAC in the study population.

Research perspectives

GRS could provide independent risk information for PDAC. Further cohort study with a larger sample size may focus on the optimal PDAC risk prediction model built with both GRS and nongenetic factors.

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