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ORIGINAL RESEARCH

Association between NR5A2 and the risk of pancreatic cancer, especially among Caucasians: a meta-analysis of case–control studies

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Background: Previous studies have reported that nuclear receptor subfamily 5, group A, member 2 (NR5A2) polymorphisms (rs3790843 G>A, rs3790844 T>C, rs12029406 C>T) are associated with the risk of pancreatic cancer. However, the results of epidemiological investigations are still controversial. In order to explore its potential attributing factors, we pooled the updated literatures to evaluate the association between NR5A2 polymorphism and the risk of pancreatic cancer in this meta-analysis.

Materials and methods: Databases such as PubMed, Google Scholar and China National Knowledge Infrastructure were searched for eligible articles following strict inclusion and exclusion criteria (updated to November 18, 2017). Odds ratios (ORs) and 95% CIs were computed to assess the intensity of association. In addition, heterogeneity, sensitivity analysis and publication bias were explored. All statistical analyses were conducted by STATA 14.0.

Results: Our results showed that the rs3790843 (GA vs GG: OR=0.86, CI=0.76–0.98, P=0.992; GA+AA vs GG: OR=0.83, CI=0.73–0.94, P=0.950; A vs G: OR=0.85, CI=0.78–0.93, P=0.802), rs3790844 (CC vs TT: OR=0.65, CI=0.54–0.78, P=0.617; CC vs TT+CT: OR=0.73, CI=0.62–0.85, P=0.742; C vs T: OR=0.78, CI=0.73–0.84, P=0.555) and rs12029406 (TT vs CC: OR=0.73, CI=0.61–0.89, P=0.483; TT vs CC+CT: OR=0.78, CI=0.66–0.92, P=0.648; T vs C: OR=0.87, CI=0.79–0.95, P=0.837) polymorphisms were associated statistically with the risk of pancreatic cancer. Furthermore, the results of subgroup analysis showed that rs3790843 and rs3790844 polymorphisms were especially related to the risk of pancreatic cancer in Caucasian population.

Conclusion: Our results revealed that NR5A2 may have a protective effect on pancreatic cancer. However, more well-designed researches are needed to verify the relationship between NR5A2 polymorphisms and the risk of pancreatic cancer.

Keywords: NR5A2, polymorphism, rs3790844, pancreatic cancer, meta-analysis

Introduction

Pancreatic cancer is a highly aggressive and malignant tumor, in which the most frequent type of tissue is ductal adenocarcinoma.[1] In the USA, about 85% of pancreatic cancer patients had already developed metastasized or unresectable lesions at the time of diagnosis and were expected to live 12 months at most.[2,3] The mortality rates are still rising in our country (China).[4] Although the cause of pancreatic cancer is not yet clear, its high mortality rate is closely related to the biologic characteristics of the tumor and the genetic factors.[5] It has been shown that 10% of pancreatic cancer is caused by genetic mutations.[6] Meanwhile, levels of molecular markers can be used to predict the prognosis of pancreatic cancer.[7]

Nuclear receptor subfamily 5, group A, member 2 (NR5A2), also called as liver receptor homolog-1, is a member of orphan nuclear hormone receptors, which is highly expressed in the pancreas, liver, intestine and ovary and is involved in the balance of cholesterol, steroidogenesis and bile acid in the body.[8,9] NR5A2 is located on chromosome 1q32.1, which is reported to play an important role in the stability of the pancreatic acinar cell.[10] Murtaugh reported that the lack of NR5A2 will promote the mutation of *Kras* gene which can accelerate deterioration of pancreatic cancer.[11] Human genome-wide association studies have suggested that there is a significant association between single-nucleotide polymorphisms (SNPs) of NR5A2 and the risk of pancreatic cancer.[12] Among these SNPs, rs3790844 is the focus of our study.

Located in the first intron of NR5A2, the SNP rs3790843 is characterized by G>A, while rs3790844 is characterized by T>C.[13] The SNP rs12029406, which is characterized by C>T, might influence the receptor activity, which, in turn, can change the disease risk and survival.[20] After searching the databases, we found five articles focusing on the association between their polymorphisms and the risk of pancreatic cancer.[18–22] In order to get rid of the limitations of a single trial and gain a result of comprehensive meaning, we combined the five studies using meta-analysis to confirm whether rs3790843, rs3790844 and rs12029406 polymorphisms would affect the risk of pancreatic cancer, which has never been done before.

Materials and methods
Literature search
We searched for relevant publications using the following words and terms: "NR5A2", "polymorphism/variety" and "pancreatic cancer/pancreatic ductal adenocarcinoma" in databases such as PubMed, Google Scholar and the China National Knowledge Infrastructure, and all literatures were published before November 18, 2017. References to these literatures were also screened in order to prevent loss of any valuable data.

Inclusion and exclusion criteria
Eligible studies were selected according to the following inclusion criteria: 1) focusing on the association between NR5A2 polymorphism and the risk of pancreatic cancer, 2) a case–control study, 3) providing available and sufficient data of genotype frequencies for calculating an odds ratio (OR) with 95% CI and 4) distribution of the genotype in case and control groups was in Hardy–Weinberg equilibrium (HWE).

The exclusion criteria were as follows: 1) non-case–control, pure cell or animal studies, 2) not related to the risk of pancreatic cancer and 3) not containing useful genotype frequency data.

Data extraction
Two authors (Q Chen, H Yuan) independently screened the literatures, extracted the relevant information and finally discussed disagreement. All the data were recorded in the standard form: first author's name, year of publication, country of population, control source, genotypic methods, number of genotypes in case–control groups and result of the HWE test. We set the total data of the case and control groups >1,000 as "sample size Y" and <1,000 as "sample size N". In addition, we classified the populations from USA, England and Germany as Caucasian, while those from China and Japan were identified as Asian for subgroup analysis.

Genetic model
A is the mutant allele of rs3790844 which includes two alleles G and A, C is the mutant allele of rs3790844 and T is the mutant allele of rs12029406. We selected the heterozygous model (GA vs GG or CT vs TT or CT vs CC), homozygous model (AA vs GG or CC vs TT or TT vs CC), dominant model (GA+AA vs GG or CT+CC vs TT or CT+TT vs CC), recessive model (AA vs GG+GA or CC vs TT+CT or TT vs CC+CT) and allele model (A vs G or C vs T or T vs C) for further meta-analysis.

Statistical analysis
Our meta-analysis was conducted by Stata software (version 14.0; StataCorp LP, College Station, TX, USA). To assess the strength of association between NR5A2 polymorphism and the risk of pancreatic cancer, we calculated the OR together with 95% CI for each genetic model. Furthermore, we evaluated the heterogeneity by Cochran's Q-statistic.[14] A P-value <0.1 indicated significant heterogeneity. Another method to evaluate the heterogeneity is I^2, which represents the percentage of variance across the whole study. In general, values of I^2 <25% represent "low heterogeneity", while values >75% represent "high heterogeneity".[15] Statistically, I^2 >50% indicates that the heterogeneity is significant and the random-effects model was chosen.[16] Otherwise, the fixed-effects model was used.[17] Moreover, data with similar characteristics such as source of control (HB/PB), sample size (Y/N) and ethnicity of the population (Asian/Caucasian) were used for subgroup analysis.

Sensitivity analyses were performed to assess the stability of the studies on the pooled ORs. A single study in the analysis was omitted each time to calculate the outcomes again. Publication bias was evaluated by using Begg's test and Egger's test, and $P<0.05$ indicated significant bias. HWE was checked by the goodness-of-fit chi-square test, and $P>0.05$ indicated the genetic balance of the population and that the data were from the same Mendelian group.

Results

Literature selection and study characteristics

The procedure of literature screening is shown in Figure 1. We found 24 articles related to NR5A2 polymorphism from PubMed, Google Scholar and China National Knowledge Infrastructure. According to the inclusion and exclusion criteria, 19 articles were excluded. Among the selected articles, 3 articles were reviews, 6 articles were not associated with the risk of pancreatic cancer and the other 10 articles lacked usable data for estimating an OR with 95% CI. Ultimately, a total of five literatures were included in the meta-analysis.[18–22] Among them, four studies containing 2,212 cases and 2,932 controls surveyed the association between rs3790843 G>A and pancreatic cancer risk, five articles on the relation between rs3790844 T>C and pancreatic cancer risk included 4,191 cases and 5,133 controls, and three publications containing 1,822 cases and 2,510 controls

explored the correlation of rs12029406 C>T with pancreatic cancer risk. One of the articles studied the association between NR5A2 polymorphism and the risk of pancreatic cancer not only from England but also from Germany with different genotyping methods.[20] Data for different controls from the same study were considered as a separate data set, which can be used for all analyses. Study characteristics of each literature are shown in Table 1.

NR5A2 rs3790843, rs3790844 and rs12029406 polymorphisms

We first analyzed the association between rs3790843, rs3790844 and rs12029406 polymorphisms and the risk of pancreatic cancer in the overall population, and the forest plots are shown in Figures 2–4. Then, in order to explain the relationship between their polymorphisms and the risk of pancreatic cancer, we also performed the subgroup analyses by control source, sample size and ethnicity. All results are presented in Table 2 in detail.

Overall effects for meta-analysis

Of the studies, two articles suggested the association between rs3790843 G>A and pancreatic cancer risk, three studies revealed an obvious association between rs3790844 T>C and pancreatic cancer risk and one research showed the association between rs12029406 C>T and pancreatic
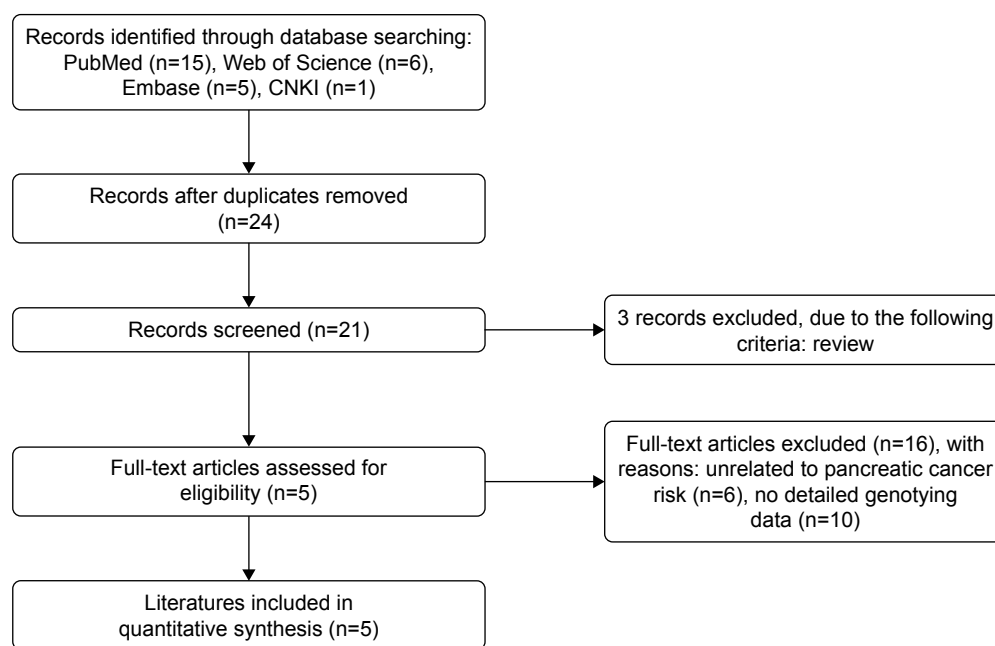

Figure 1 Flowchart of the literature selection process.
Abbreviation: CNKI, China National Knowledge Infrastructure.

Table 1 Characteristics of the five studies included in the meta-analysis

Author	Year	Country	Control source	Case			Control			Sample size[a]	Biologic sample	Genotyping method	Completion[b]	HWE
rs3790843				**GG**	**AG**	**AA**	**GG**	**AG**	**AA**					
1 Makoto et al[18]	2015	Japan	HB	30	155	175	25	157	218	N	Blood	Fluidgm	Y	0.64
2 Hongwei et al[19]	2011	USA	HB	552	410	79	541	478	114	Y	Blood	TapMan	Y	0.81
3 Cosmeri et al[20]														
Liverpool	2011	England	PB	60	43	7	72	55	9	N	Tissue/blood	KASPar/Beadchip	N	0.85
Heidelberg	2011	Germany	PB	324	216	34	594	454	88	Y	Tissue/blood	KASPar	N	0.8
4 Yao[22]	2013	China	PB	11	56	60	11	58	58	N	Blood	TapMan	N	0.84
rs3790844				**TT**	**CT**	**CC**	**TT**	**CT**	**CC**					
1 Makoto et al[18]	2015	Japan	HB	40	165	155	27	163	210	N	Blood	Fluidgm	Y	0.54
2 Hongwei et al[19]	2011	USA	HB	670	330	55	652	409	75	Y	Blood	TapMan	Y	0.32
3 Cosmeri et al[20]														
Liverpool	2011	England	PB	71	34	4	85	46	5	N	Tissue/blood	KASPar/Beadchip	N	0.69
Heidelberg	2011	Germany	PB	343	166	25	671	398	57	Y	Tissue/blood	KASPar	N	0.84
4 Alison et al[21]	2013	USA	HB	1,319	605	82	1,273	798	137	Y	–	Illumina	Y	0.43
5 Yao[22]	2013	China	PB	11	63	53	9	61	57	N	Blood	TapMan	N	0.22
rs12029406				**CC**	**CT**	**TT**	**CC**	**CT**	**TT**					
1 Hongwei et al[19]	2011	USA	HB	401	517	137	401	534	198	Y	Blood	TapMan	Y	0.14
2 Cosmeri et al[20]														
Liverpool	2011	England	PB	45	42	12	55	63	18	N	Tissue/blood	KASPar/Beadchip	N	0.65
Heidelberg	2011	Germany	PB	217	242	82	406	521	187	Y	Tissue/blood	KASPar	N	0.29
3 Yao[22]	2013	China	PB	7	50	70	2	46	79	N	Blood	TapMan	N	0.81

Notes: [a]"Y" the total sample size is larger than 1,000; "N" the total sample size is smaller than 1,000. [b]"Y" the rs3790844 polymorphism is associated with the risk of pancreatic cancer; "N" the rs3790844 polymorphism is not associated with the risk of pancreatic cancer. $P>0.05$ means the population was from the same Mendelian population.
Abbreviations: HB, hospital-based; HWE, Hardy–Weinberg equilibrium; PB, population-based.
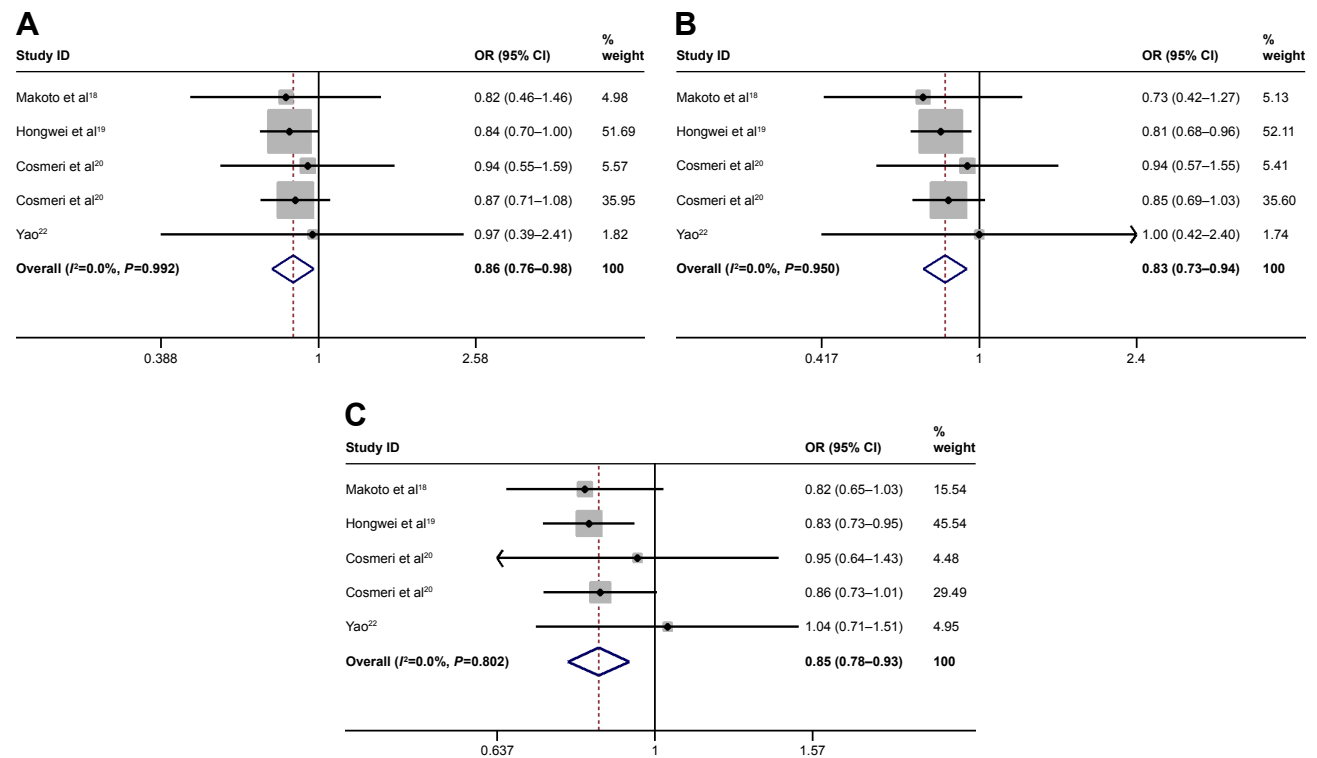
Figure 2 Forest plots of pancreatic cancer risk associated with NR5A2 rs3790843 G>A polymorphism.
Notes: (**A**) GA vs GG; (**B**) GA+AA vs GG; (**C**) A vs G.
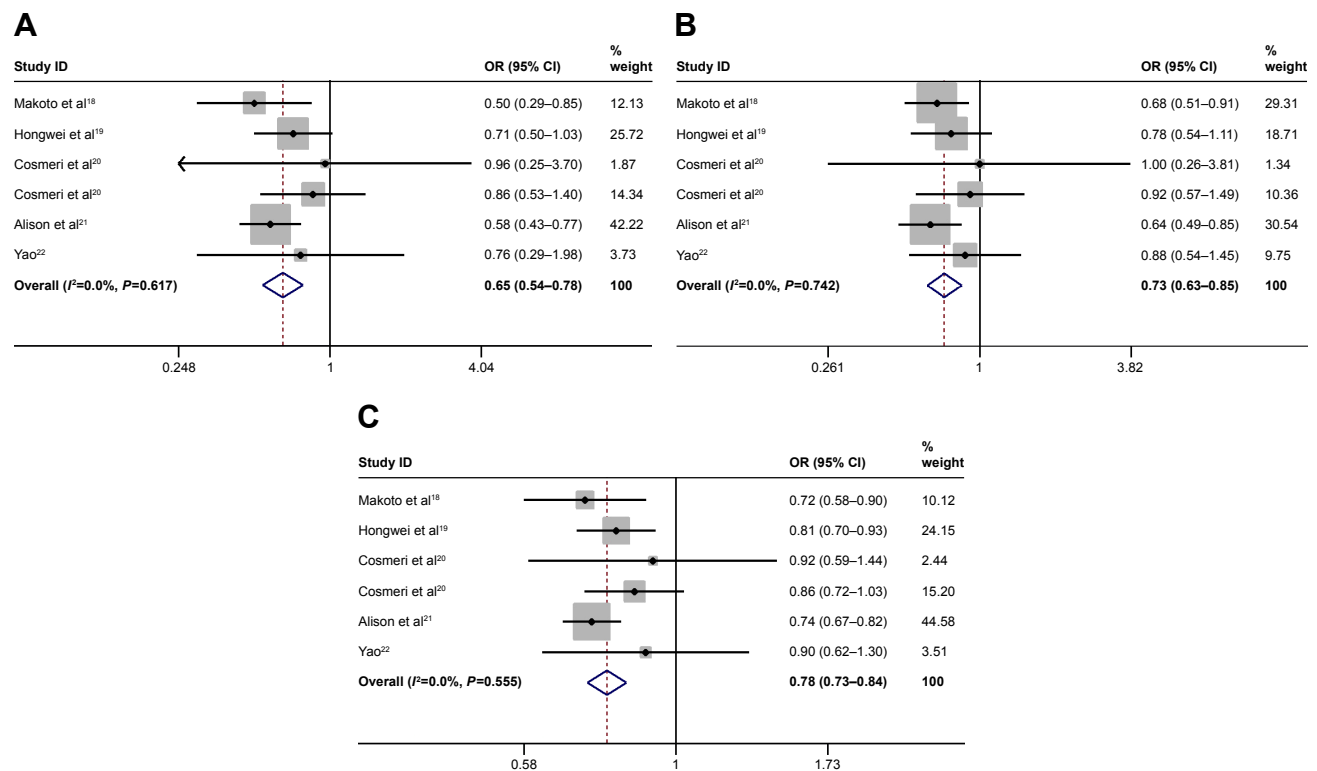**Abbreviation:** OR, odds ratio.

Figure 3 Forest plots of pancreatic cancer risk associated with NR5A2 rs3790844 T>C polymorphism.
Notes: (**A**) CC vs TT; (**B**) CC vs TT+CT; (**C**) C vs T. Weights are from random-effects analysis.
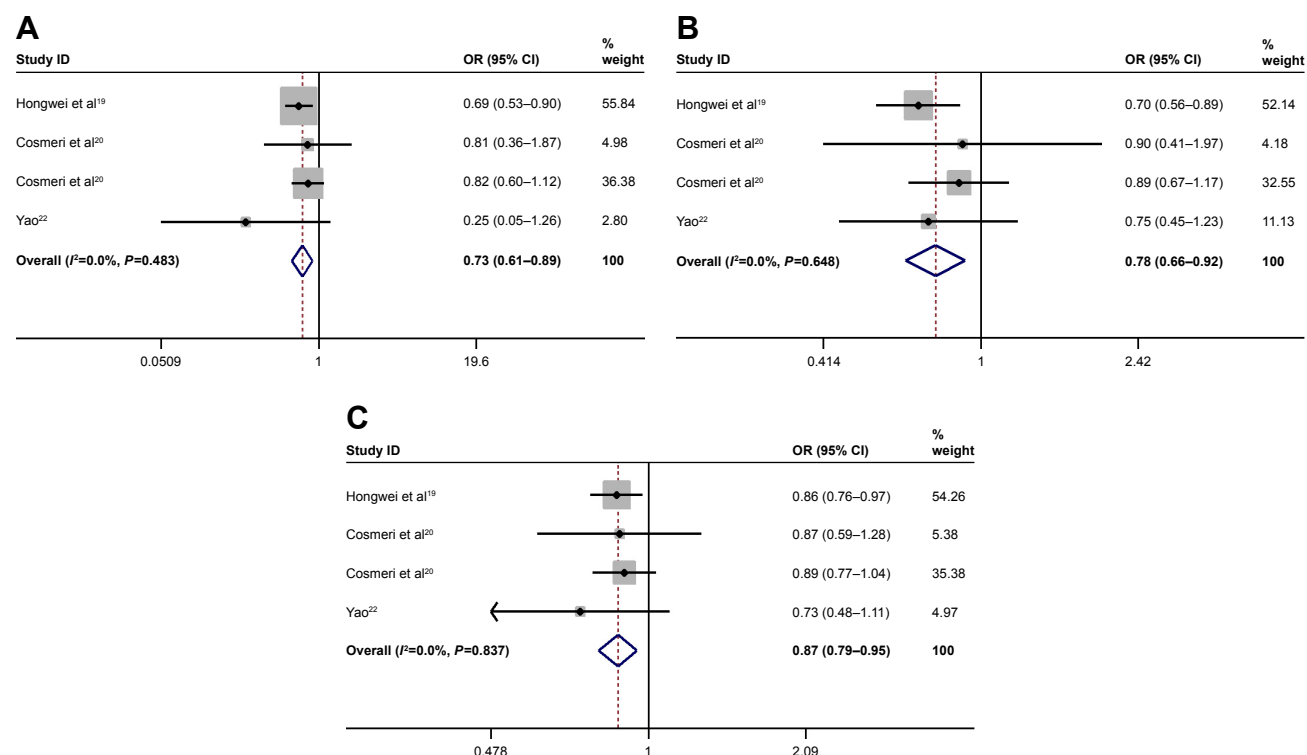**Abbreviation:** OR, odds ratio.

Figure 4 Forest plots of pancreatic cancer risk associated with NR5A2 rs12029406 C>T polymorphism.
Notes: (**A**) TT vs CC; (**B**) TT vs CC+CT; (**C**) T vs C.
Abbreviation: OR, odds ratio.

cancer risk. After analyzing the existing data, we found a significant association between rs3790843 polymorphism (GA vs GG: OR=0.86, CI=0.76–0.98, P=0.992; GA+AA vs GG: OR=0.83, CI=0.73–0.94, P=0.950; A vs G: OR=0.85, CI=0.78–0.93, P=0.802; Figure 2), rs3790844 polymorphism (CC vs TT: OR=0.65, CI=0.54–0.78, P=0.617; CC vs TT+CT: OR=0.73, CI=0.62–0.85, P=0.742; C vs T: OR=0.78, CI=0.73–0.84, P=0.555; Figure 3) and rs12029406 polymorphism (TT vs CC: OR=0.73, CI=0.61–0.89, P=0.483; TT vs CC+CT: OR=0.78, CI=0.66–0.92, P=0.648; T vs C: OR=0.87, CI=0.79–0.95, P=0.837; Figure 4) and the risk of pancreatic cancer susceptibility.

Subgroup analysis for control source

Subgroup analysis was stratified by control sources. Statistically significant association between rs3790843 (GA vs GG: OR=0.84, CI=0.71–0.99, P=0.944; GA+AA vs GG: OR=0.80, CI=0.68–0.94, P=0.737; A vs G: OR=0.83, CI=0.74–0.93, P=0.934; Figure S1) and rs3790844 (CC vs TT: OR=0.61, CI=0.49–0.74, P=0.495; CC vs TT+CT: OR=0.69, CI=0.58–0.82, P=0.718; C vs T: OR=0.76, CI=0.70–0.82, P=0.559; Figure S2) polymorphisms with the risk of pancreatic cancer was detected in hospital-based studies under five genetic models.

Subgroup analysis for sample size

The sample size with sufficient statistical capacity is critical to the study and for the relationship between polymorphisms and the risk of cancer. We set the total data >1,000 as "Y" and <1,000 as "N". Statistically significant association between rs3790843 (GA vs GG: OR=0.85, CI=0.75–0.98, P=0.793; GA+AA vs GG: OR=0.82, CI=0.72–0.94, P=0.745; A vs G: OR=0.84, CI=0.76–0.93, P=0.757; Figure S3) and rs3790844 (CC vs TT: OR=0.66, CI=0.54–0.82, P=0.344; CC vs TT+CT: OR=0.73, CI=0.63–0.85, P=0.411; C vs T: OR=0.78, CI=0.72–0.85, P=0.300; Figure S4) polymorphisms and the risk of pancreatic cancer was also detected in "Y"-based studies under five genetic models.

Subgroup analysis for ethnicity

Subgroup analysis was stratified by ethnicity. The relationship between rs3790843 (GA vs GG: OR=0.86, CI=0.76–0.98, P=0.912; GA+AA vs GG: OR=0.83, CI=0.73–0.94, P=0.843; A vs G: OR=0.85, CI=0.77–0.93, P=0.798; Figure 5) and rs3790844 (CC vs TT: OR=0.67, CI=0.55–0.82, P=0.491; CC vs TT+CT: OR=0.73, CI=0.60–0.89, P=0.575; C vs T: OR=0.78, CI=0.73–0.85, P=0.404; Figure 6) polymorphisms and the risk of pancreatic cancer was detected from the data of Caucasian population.

Table 2 Meta-analysis results of association between NR5A2 polymorphism and pancreatic cancer risk

rs3790843		GA vs GG			AA vs GG			GA+AA vs GG			AA vs GG+GA			A vs G		
Variables	n[a]	OR (95% CI)	P-value[b]	I² (%)	OR (95% CI)	P-value[b]	I² (%)	OR (95% CI)	P-value[b]	I² (%)	OR (95% CI)	P-value[b]	I² (%)	OR (95% CI)	P-value[b]	I² (%)
Total	5	0.86 (0.76–0.98)	0.992	0.0	0.71 (0.57–0.88)	0.904	0.0	0.83 (0.73–0.94)	0.950	0.0	0.80 (0.67–0.94)	0.766	0.0	0.85 (0.78–0.93)	0.802	0.0
Control source																
HB	2	0.84 (0.71–0.99)	0.944	0.0	0.68 (0.52–0.89)	0.963	0.0	0.80 (0.68–0.94)	0.737	0.0	0.76 (0.62–0.94)	0.729	0.0	0.83 (0.74–0.93)	0.934	0.0
PB	3	0.89 (0.73–1.07)	0.951	0.0	0.77 (0.57–0.88)	0.710	0.0	0.86 (0.72–1.04)	0.882	0.0	0.87 (0.65–1.17)	0.552	0.0	0.89 (0.78–1.02)	0.618	0.0
Sample size[c]																
N	3	0.90 (0.63–1.28)	0.933	0.0	0.78 (0.51–1.21)	0.682	0.0	0.86 (0.61–1.21)	0.760	0.0	0.86 (0.67–1.09)	0.574	0.0	0.89 (0.75–1.06)	0.532	0.0
Y	2	0.85 (0.75–0.98)	0.793	0.0	0.69 (0.54–0.89)	0.874	0.0	0.82 (0.72–0.94)	0.745	0.0	0.74 (0.58–0.94)	0.934	0.0	0.84 (0.76–0.93)	0.757	0.0
Ethnicity																
Asian	2	0.86 (0.53–1.40)	0.771	0.0	0.76 (0.47–1.22)	0.426	0.0	0.80 (0.50–1.28)	0.556	0.0	0.85 (0.67–1.09)	0.303	5.7	0.87 (0.72–1.06)	0.292	9.9
Caucasian	3	0.86 (0.76–0.98)	0.912	0.0	0.70 (0.55–0.89)	0.848	0.0	0.83 (0.73–0.94)	0.843	0.0	0.75 (0.59–0.95)	0.886	0.0	0.85 (0.77–0.93)	0.798	0.0

rs3790844		CT vs TT			CC vs TT			CT+CC vs TT			CC vs TT+CT			C vs T		
Variables	n[a]	OR (95% CI)	P-value[b]	I² (%)	OR (95% CI)	P-value[b]	I² (%)	OR (95% CI)	P-value[b]	I² (%)	OR (95% CI)	P-value[b]	I² (%)	OR (95% CI)	P-value[b]	I² (%)
Total	6	0.76 (0.70–0.84)	0.932	0.0	0.65 (0.54–0.78)	0.617	0.0	0.75 (0.68–0.81)	0.699	0.0	0.73 (0.62–0.85)	0.742	0.0	0.78 (0.73–0.84)	0.555	0.0
Control source																
HB	3	0.75 (0.67–0.83)	0.781	0.0	0.61 (0.49–0.74)	0.495	0.0	0.73 (0.66–0.80)	0.491	0.0	0.69 (0.58–0.82)	0.718	0.0	0.76 (0.70–0.82)	0.559	0.0
PB	3	0.83 (0.68–1.01)	0.963	0.0	0.85 (0.56–1.28)	0.959	0.0	0.83 (0.68–1.00)	0.958	0.0	0.91 (0.65–1.27)	0.981	0.0	0.87 (0.75–1.02)	0.953	0.0
Sample size[c]																
N	3	0.79 (0.55–1.12)	0.791	0.0	0.58 (0.38–0.91)	0.562	0.0	0.73 (0.52–1.02)	0.499	0.0	0.74 (0.58–0.94)	0.624	0.0	0.79 (0.66–0.94)	0.460	0.0
Y	3	0.76 (0.70–0.84)	0.658	0.0	0.66 (0.54–0.82)	0.344	6.2	0.75 (0.68–0.82)	0.452	0.0	0.73 (0.63–0.85)	0.411	0.0	0.78 (0.72–0.85)	0.300	16.9
Ethnicity																
Asian	2	0.72 (0.45–1.15)	0.702	0.0	0.55 (0.35–0.88)	0.448	0.0	0.63 (0.40–0.98)	0.540	0.0	0.73 (0.57–0.93)	0.390	0.0	0.76 (0.63–0.92)	0.322	0.0
Caucasian	4	0.77 (0.70–0.84)	0.772	0.0	0.67 (0.55–0.82)	0.491	0.0	0.75 (0.68–0.81)	0.569	0.0	0.73 (0.60–0.89)	0.575	0.0	0.78 (0.73–0.85)	0.404	0.0

rs12029406		CT vs CC			TT vs CC			CT+TT vs CC			TT vs CC+CT			T vs C		
Variables	n[a]	OR (95% CI)	P-value[b]	I² (%)	OR (95% CI)	P-value[b]	I² (%)	OR (95% CI)	P-value[b]	I² (%)	OR (95% CI)	P-value[b]	I² (%)	OR (95% CI)	P-value[b]	I² (%)
Total	4	0.91 (0.80–1.05)	0.487	0.0	0.73 (0.61–0.89)	0.483	0.0	0.87 (0.76–0.99)	0.533	0.0	0.78 (0.66–0.92)	0.648	0.0	0.87 (0.79–0.95)	0.837	0.0

Notes: [a]Number of studies. [b]P-value of Q-test for heterogeneity. [c]"Y" the total sample size is larger than 1,000; "N" the total sample size is smaller than 1,000.
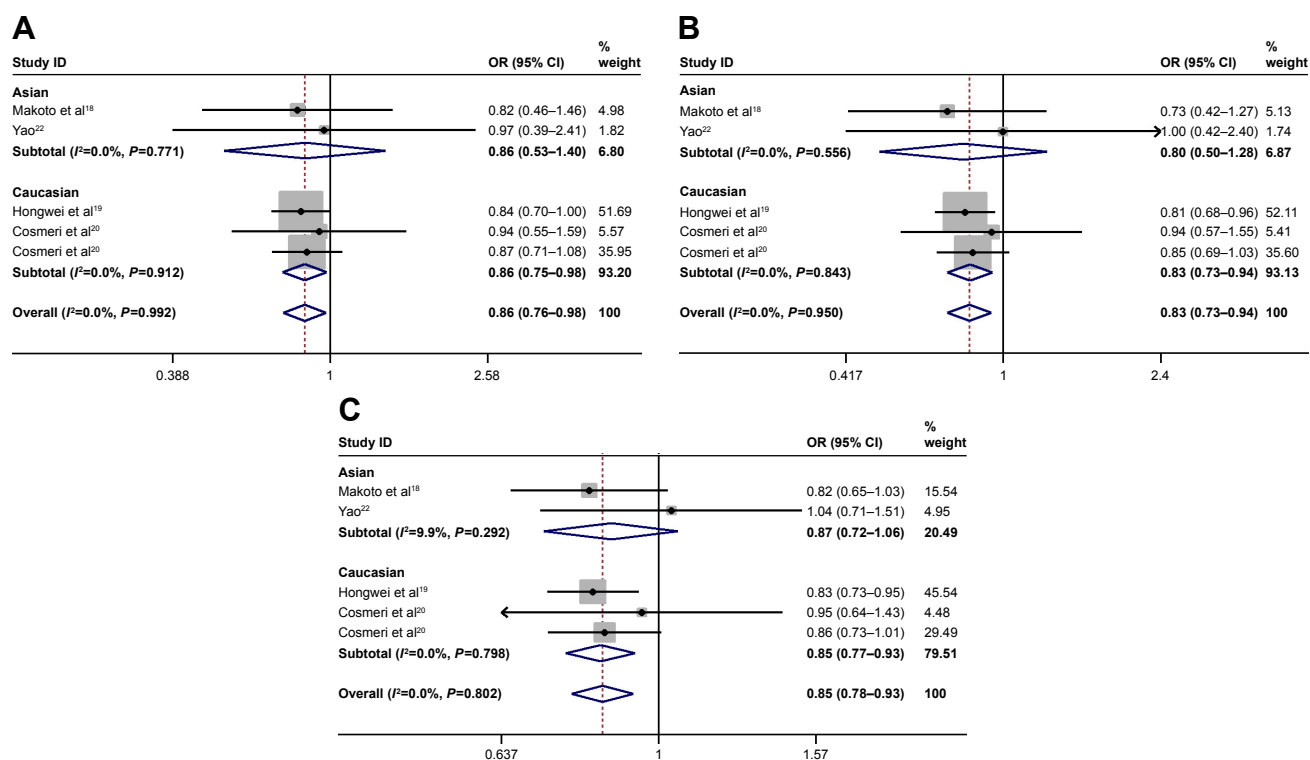**Abbreviations:** HB, hospital-based; OR, odds ratio; PB, population-based.

Figure 5 Subgroup analysis of ethnicity for NR5A2 rs3790843 G>A polymorphism and pancreatic cancer risk.
Notes: (**A**) GA vs GG; (**B**) GA+AA vs GG; (**C**) A vs G.
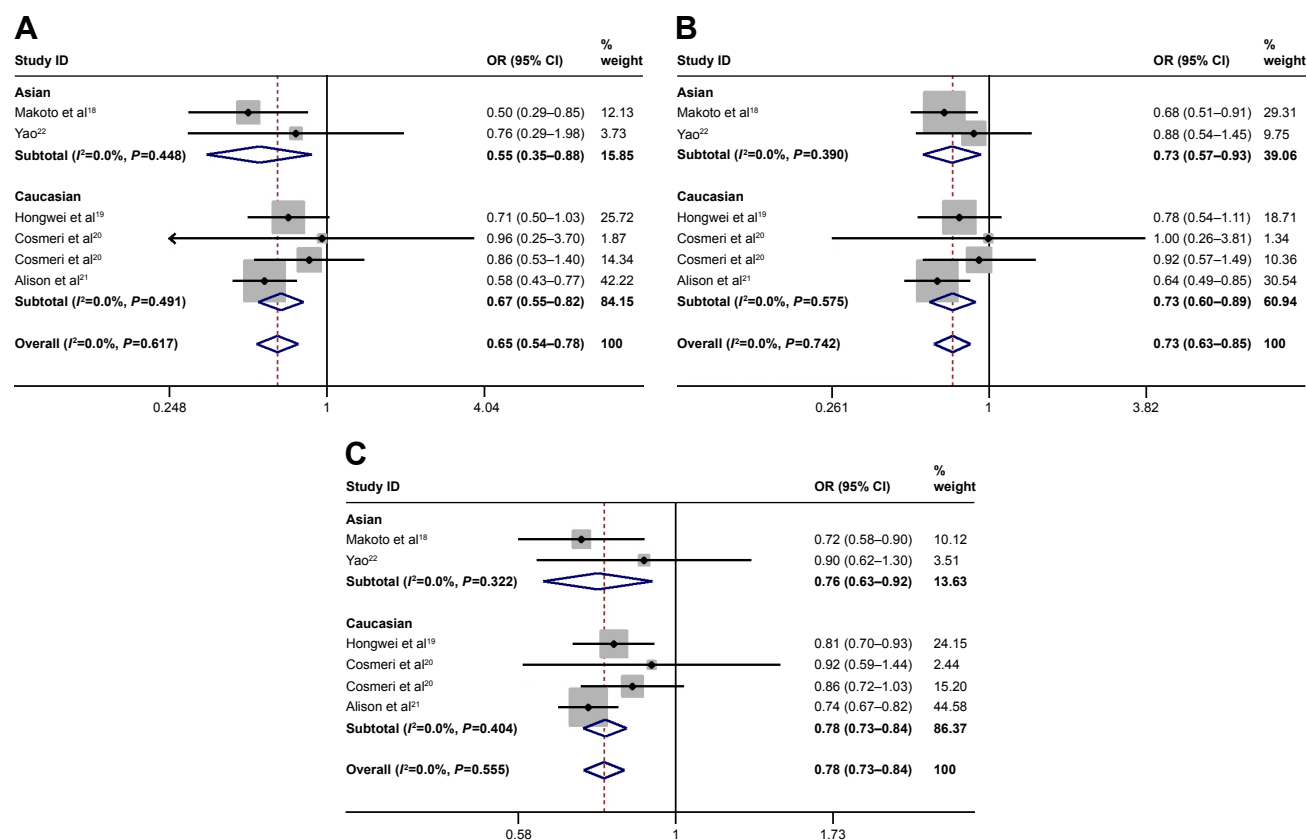**Abbreviation:** OR, odds ratio.

Figure 6 Subgroup analysis of ethnicity for NR5A2 rs3790844 T>C polymorphism and pancreatic cancer risk.
Notes: (**A**) CC vs TT; (**B**) CC vs TT+CT; (**C**) C vs T. Weights are from random-effects analysis.
Abbreviation: OR, odds ratio.

Table 3 The results of Begg's and Egger's tests

| Risk model | rs3790843 | | | | rs3790844 | | | | rs12029406 | | | |
| | Begg's test | | Egger's test | | Begg's test | | Egger's test | | Begg's test | | Egger's test | |
	Z	P-value	Z	P-value	Z	P-value	t	P-value	Z	P-value	t	P-value
Heterozygous	0.73	0.462	1.22	0.311	0.38	0.707	0.89	0.426	1.02	0.308	−2.91	0.101
Homozygous	1.22	0.221	2.76	0.070	0.00	1.000	0.92	0.408	0.34	0.734	−0.81	0.501
Dominant	0.24	0.806	0.76	0.503	0.38	0.707	0.36	0.735	1.70	0.089	−3.05	0.093
Recessive	0.73	0.462	1.28	0.292	1.50	0.133	2.35	0.079	0.34	0.734	0.50	0.668
Allele	1.22	0.221	2.45	0.091	0.75	0.452	1.55	0.196	0.34	0.734	−0.99	0.428

Heterogeneity test

Based on the Cochran's Q-statistic, all the data showed nonsignificant heterogeneity under five genetic models (Table 2).

Sensitivity analysis

In order to compare the differences and assess the sensitivity, a single study in the analysis was omitted each time to calculate the outcomes again. The pooled ORs were not influenced significantly, which indicated our results of this meta-analysis were stable (Figure S5).

Publication bias analysis

To evaluate the publication bias of the publications, Begg's test and Egger's test were performed. The funnel plots of five genetic models whose shapes were roughly symmetrical suggested no significant publication bias (figure not shown). Moreover, the results shown in Table 3 indicate that our results were reliable.

Discussion

As a highly malignant disease, pancreatic cancer is the fourth leading cause of cancer death in the USA.[23] Most patients would have already progressed to an advanced stage with a poor cure rate when diagnosed. Surgical treatment is still the first choice to cure pancreatic cancer up to now, but only 15%–20% of patients have the opportunity to take it up.[24,25] What is worse, despite surgical resection, the majority of these patients would die from recurrence or metastasis in 2 years.[26] Radiotherapy and chemotherapy, such as gemcitabine (Eli Lilly and Company, Indianapolis, IN, USA) or molecular-targeted drugs, are recommended for patients lacking the opportunity to undergo surgery.[27,28] Disappointingly, the efficacy of these drugs to increase the survival rate is barely observed and unexplainable drug resistance comes up. Different from other cancers, the 5-year survival rate of pancreatic cancer has changed just a little in the past four decades (as low as 6%).[29] It has been shown that genetic factors play an important role in the development, progression

and prognosis of pancreatic cancer.[7,30,31] Exploring the genetic background of pancreatic cancer is instructive to find out some targets which can help in early diagnosis and judge the prognosis of pancreatic cancer.

Previous studies have shown that NR5A2, which is also known as liver receptor homolog-1, is an important regulator of pancreatic exocrine function.[32] Lack of NR5A2, combined with pancreas-specific transcription factor 1 causes instability of pancreatic acinar cells, which increases the pancreatic injury and then causes mutations in the *Kras* gene.[10,32–34] As we all know, mutation of *Kras* is the earliest event in deterioration of pancreatic cancer.[11] We integrated the results of five studies and found a negative link between NR5A2 rs3790844 polymorphism and the risk of pancreatic cancer. However, histologic examinations show that NR5A2 is overexpressed in tumor tissues, which is quiet puzzling.[35] Although the mechanism is not clear, it does not deny our conclusion that NR5A2 is a protective factor for early pancreatic cancer. Here, we put forward several possible explanations for discussion. Overexpression of NR5A2 is also closely related to diabetes and hyperlipidemia, which are the important risk factors for pancreatic cancer, and has a positive effect on mutation of *Kras* later in pancreatic cancer progression.[11,36,37] Moreover, NR5A2 also contributes to other tumors. For instance, NR5A2 was reported to be involved in the metabolism of glutamine to induce hepatocellular carcinoma, while it also induces the expression and transcription of ERα and mediates the secretion of estrogen to affect the progression of breast cancer.[38–40] In addition, NR5A2 is overexpressed in colon cancer and osteosarcoma cells.[41,42] Recently, many studies have reported the relationship between the NR5A2 rs3790843, rs3790844 and rs12029406 polymorphisms and the risk of cholangiocarcinoma, gastric cancer and pancreatic cancer without consistent results.[13,18–22,43] In order to clarify the association, we integrated the data of pancreatic cancer for the meta-analysis.

The polymorphism was observed to be related with pancreatic cancer in hospital-based studies, but not in population-based studies in the subgroup analysis by the control source.

Unsurprisingly, a larger sample bounded by 1,000 was more credible than a smaller sample in the relationship between them and cancer, which suggested that future research should require a larger sample size. Moreover, the subgroup analysis by ethnicity was also performed. The association between rs3790843 and rs3790844 polymorphisms and the risk of pancreatic cancer in Caucasian population under all genetic models was statistically significant; however, this was not found in the Asian population. Different genetic background or different lifestyles may lead to this difference between them and the total population.

As far as we know, this is the first meta-analysis of the association between NR5A2 (rs3790843, rs3790844, rs12029406) polymorphisms and the risk of pancreatic cancer. The analysis showed that the GA or AA genotype reduced the risk of pancreatic cancer and the A allele reduced the risk to 0.85 compared with the rs3790843 polymorphism and the TC or CC genotype, which played a similar role in the rs3790844 polymorphism, and the C allele reduced the risk to 0.78. Moreover, the TC or TT genotype of rs12029406 could also protect from pancreatic cancer and the T allele reduced the risk to 0.87. The largest value of I^2 was 16.9% ($<25\%$), which means that no heterogeneity was found in all studies. Meanwhile, no abnormality was found in sensitivity analysis.

Limitations

There were some limitations in our meta-analysis which might have affected the final outcomes. First, the study was based on unadjusted OR values, which did not contain the well-known predisposing factors of pancreatic cancer, such as age, sex, alcohol, smoking, diabetes and chronic pancreatitis. Second, we lacked data from non-Caucasian populations in Africa in the subgroup analysis for ethnicity. Finally, different genotypic methods (Fluidgm, TapMan, KASPar and so on) could also have an impact on the outcome. More researches are needed to further analyze the association between NR5A2 polymorphism and the risk of pancreatic cancer.

Conclusion

Our study showed that the NR5RA rs3790843, rs3790844 and rs12029406 polymorphisms were favorable factors in the risk of pancreatic cancer and were more protective in Caucasian population. If the mechanism behind this could be discovered by further research, hopefully, it will become a target for future personalized treatment of pancreatic cancer. Due to the limitations shown in this analysis, larger sample size and diverse studies are needed to confirm our results.

Acknowledgment

Disclosure

The authors report no conflicts of interest in this work.

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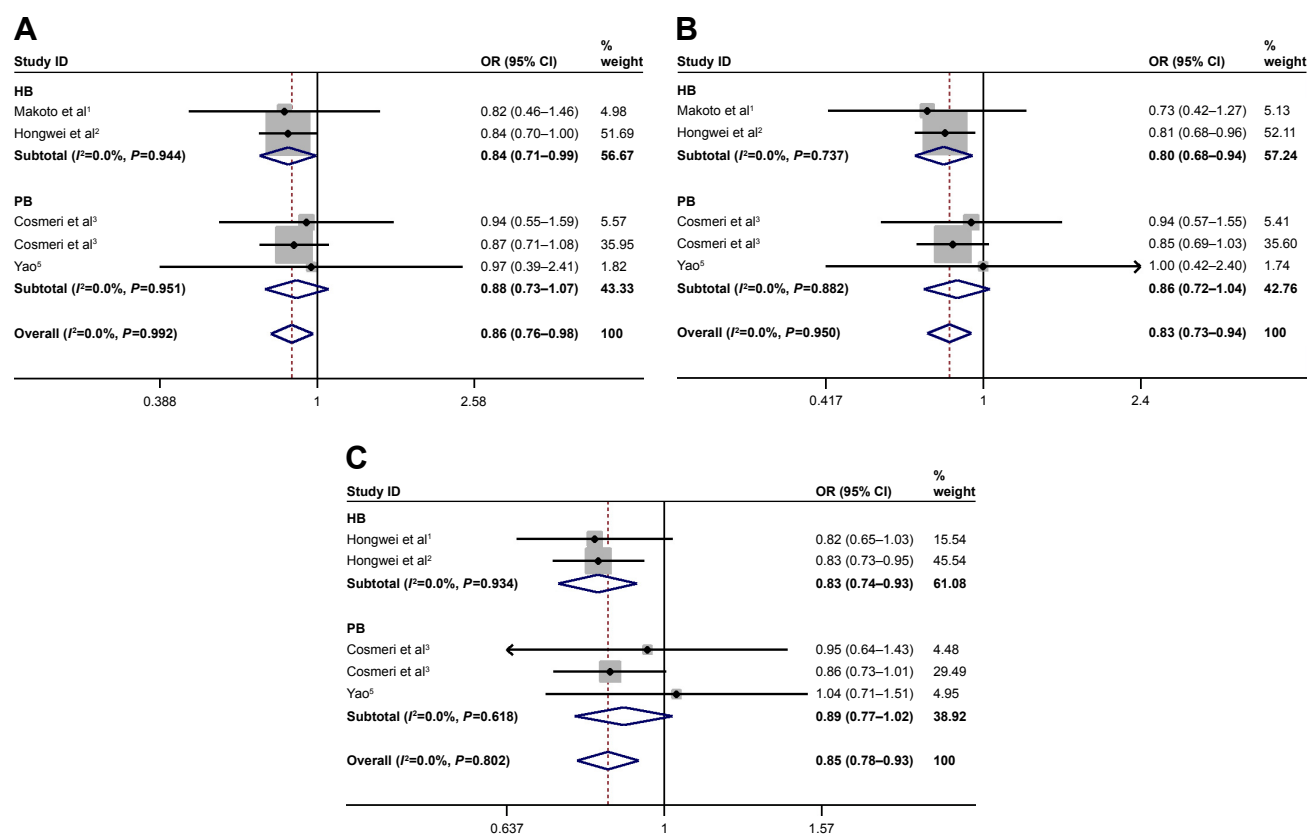
Supplementary materials

Figure S1 Subgroup analysis of type of control source for NR5A2 rs3790843 G>A polymorphism and pancreatic cancer risk.
Notes: (**A**) GA vs GG; (**B**) GA+AA vs GG; (**C**) A vs G.
Abbreviations: HB, hospital-based; OR, odds ratio; PB, population-based.

Figure S2 (*Continued*)

C

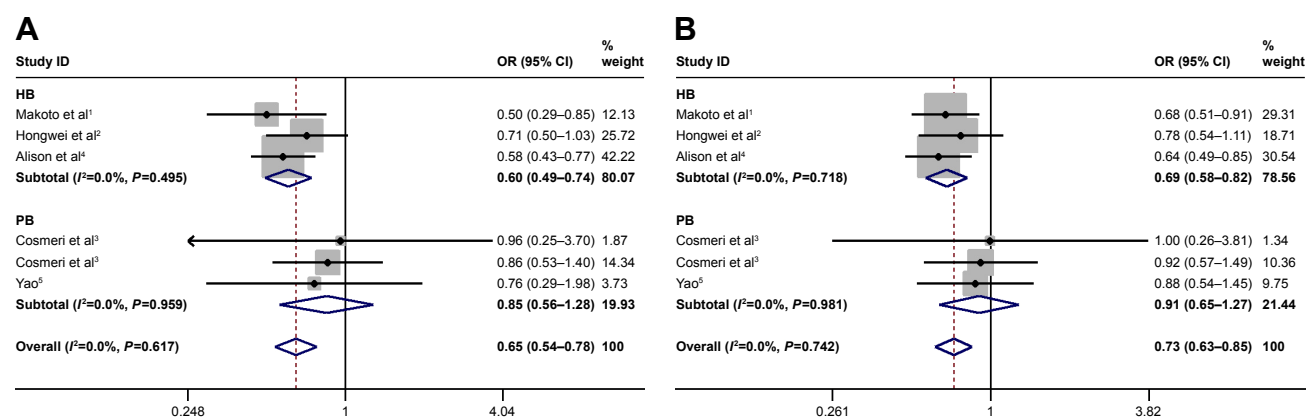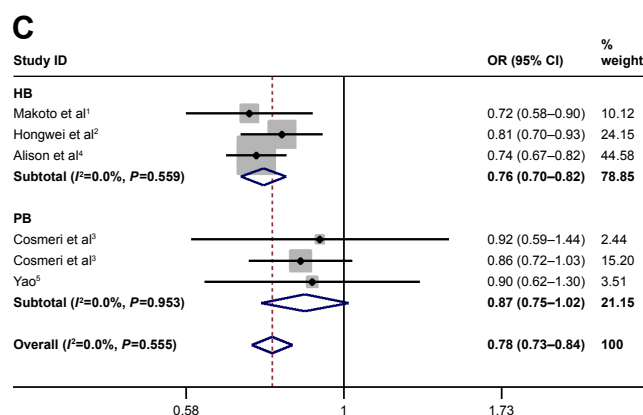| Study ID	OR (95% CI)	% weight
HB		
Makoto et al[1]	0.72 (0.58–0.90)	10.12
Hongwei et al[2]	0.81 (0.70–0.93)	24.15
Alison et al[4]	0.74 (0.67–0.82)	44.58
Subtotal (I^2=0.0%, P=0.559)	0.76 (0.70–0.82)	78.85
PB		
Cosmeri et al[3]	0.92 (0.59–1.44)	2.44
Cosmeri et al[3]	0.86 (0.72–1.03)	15.20
Yao[5]	0.90 (0.62–1.30)	3.51
Subtotal (I^2=0.0%, P=0.953)	0.87 (0.75–1.02)	21.15
Overall (I^2=0.0%, P=0.555)	0.78 (0.73–0.84)	100

0.58   1   1.73

Figure S2 Subgroup analysis of type of control source for NR5A2 rs3790844 T>C polymorphism and pancreatic cancer risk.
Notes: (**A**) CC vs TT; (**B**) CC vs TT+CT; (**C**) C vs T. Weights are from random-effects analysis.
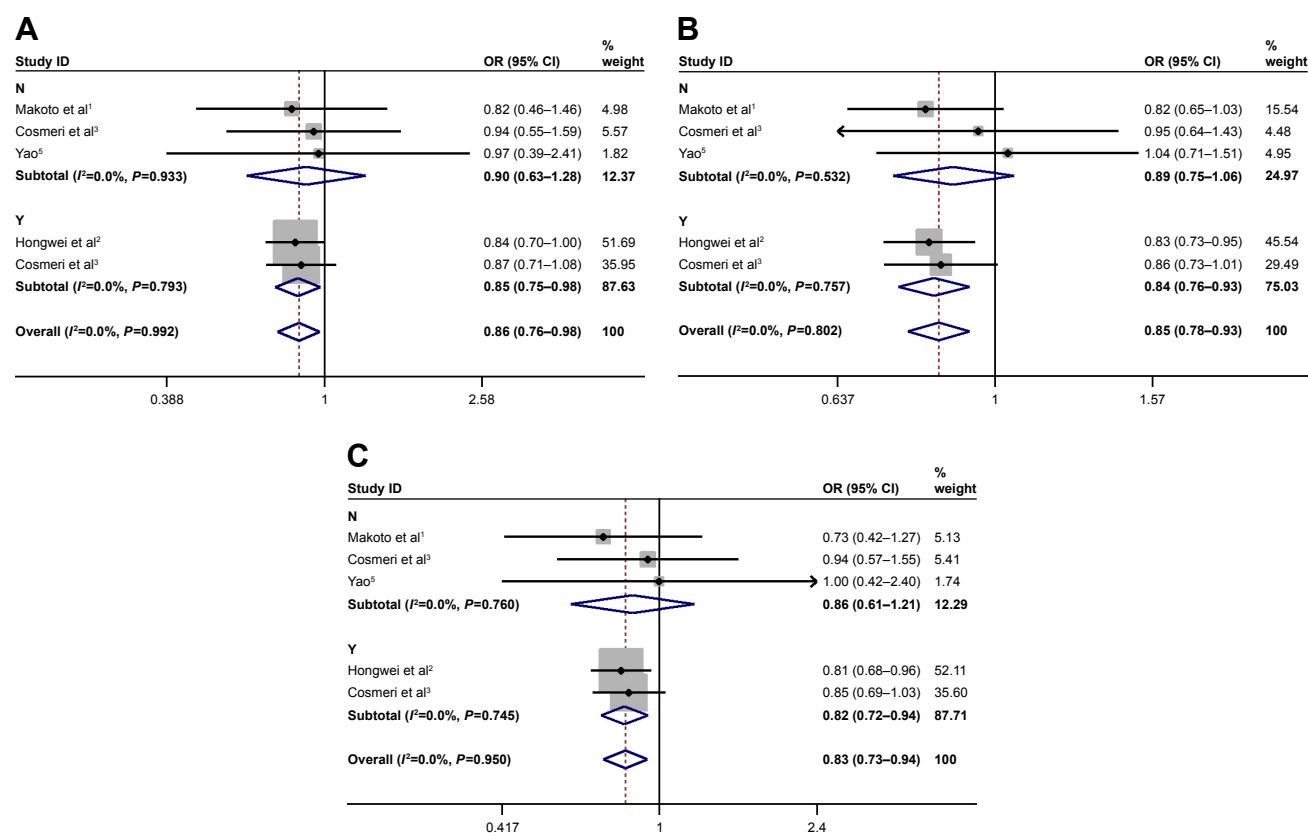**Abbreviations:** HB, hospital-based; OR, odds ratio; PB, population-based.

A

Study ID	OR (95% CI)	% weight
N		
Makoto et al[1]	0.82 (0.46–1.46)	4.98
Cosmeri et al[3]	0.94 (0.55–1.59)	5.57
Yao[5]	0.97 (0.39–2.41)	1.82
Subtotal (I^2=0.0%, P=0.933)	0.90 (0.63–1.28)	12.37
Y		
Hongwei et al[2]	0.84 (0.70–1.00)	51.69
Cosmeri et al[3]	0.87 (0.71–1.08)	35.95
Subtotal (I^2=0.0%, P=0.793)	0.85 (0.75–0.98)	87.63
Overall (I^2=0.0%, P=0.992)	0.86 (0.76–0.98)	100

0.388   1   2.58

B

Study ID	OR (95% CI)	% weight
N		
Makoto et al[1]	0.82 (0.65–1.03)	15.54
Cosmeri et al[3]	0.95 (0.64–1.43)	4.48
Yao[5]	1.04 (0.71–1.51)	4.95
Subtotal (I^2=0.0%, P=0.532)	0.89 (0.75–1.06)	24.97
Y		
Hongwei et al[2]	0.83 (0.73–0.95)	45.54
Cosmeri et al[3]	0.86 (0.73–1.01)	29.49
Subtotal (I^2=0.0%, P=0.757)	0.84 (0.76–0.93)	75.03
Overall (I^2=0.0%, P=0.802)	0.85 (0.78–0.93)	100

0.637   1   1.57

C

Study ID	OR (95% CI)	% weight
N		
Makoto et al[1]	0.73 (0.42–1.27)	5.13
Cosmeri et al[3]	0.94 (0.57–1.55)	5.41
Yao[5]	1.00 (0.42–2.40)	1.74
Subtotal (I^2=0.0%, P=0.760)	0.86 (0.61–1.21)	12.29
Y		
Hongwei et al[2]	0.81 (0.68–0.96)	52.11
Cosmeri et al[3]	0.85 (0.69–1.03)	35.60
Subtotal (I^2=0.0%, P=0.745)	0.82 (0.72–0.94)	87.71
Overall (I^2=0.0%, P=0.950)	0.83 (0.73–0.94)	100

0.417   1   2.4

Figure S3 Subgroup analysis of sample size for NR5A2 rs3790843 G>A polymorphism and pancreatic cancer risk.
Notes: (**A**) GA vs GG; (**B**) GA+AA vs GG; (**C**) A vs G. N, the total sample size is smaller than 1,000; Y, the total sample size is larger than 1,000.
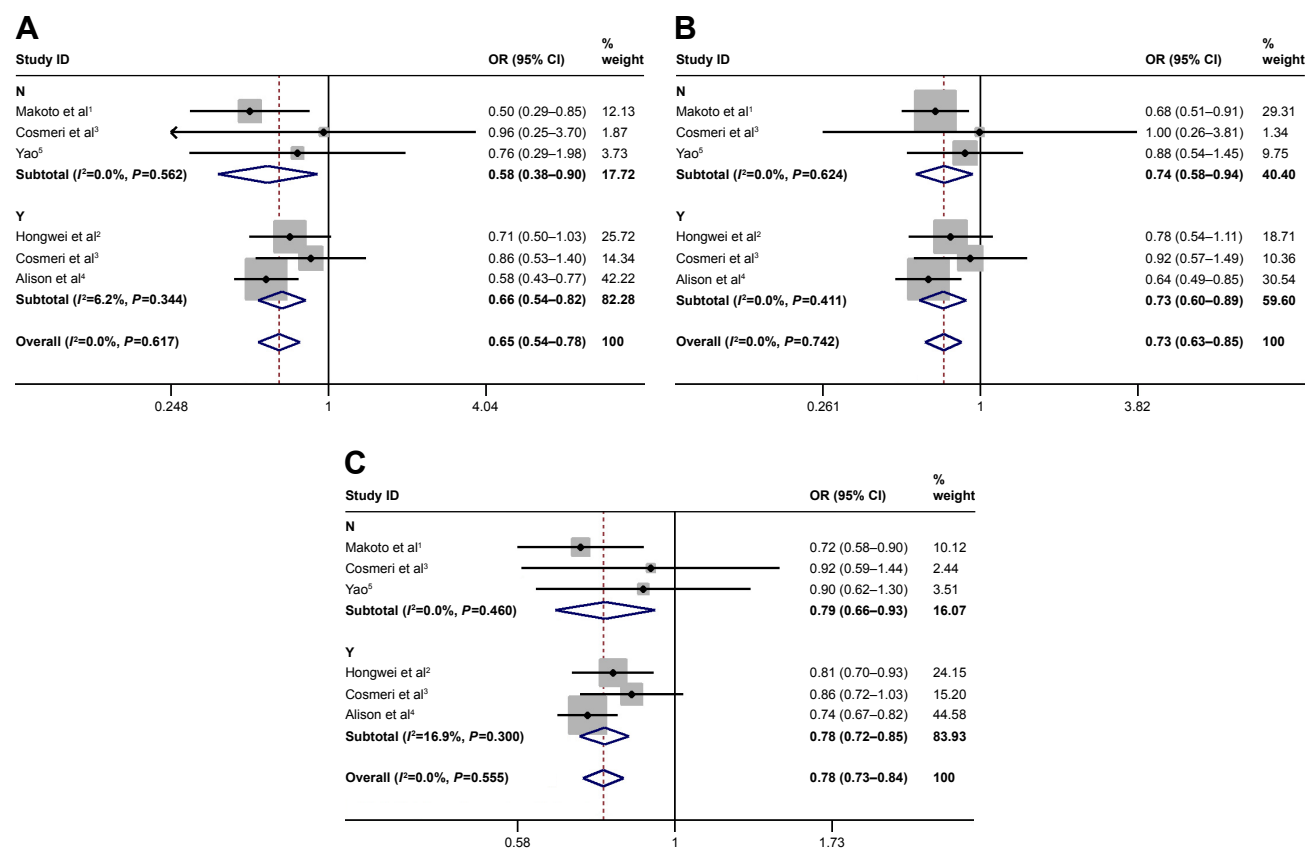**Abbreviation:** OR, odds ratio.

Figure S4 Subgroup analysis of sample size for NR5A2 rs3790844 T>C polymorphism and pancreatic cancer risk.
Notes: (**A**) CC vs TT; (**B**) CC vs TT+CT; (**C**) C vs T. N, the total sample size is smaller than 1,000; Y, the total sample size is larger than 1,000. Weights are from random-effects analysis.
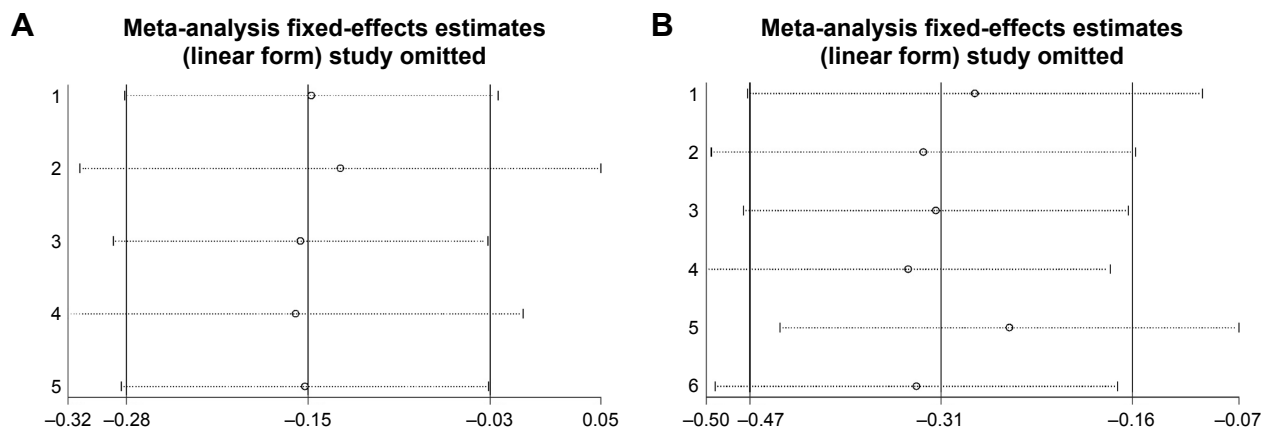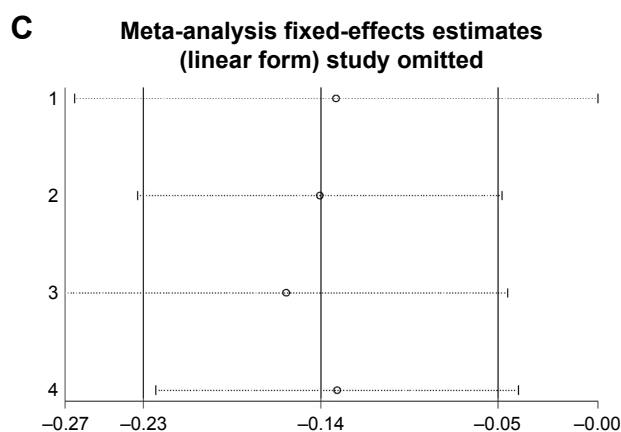**Abbreviation:** OR, odds ratio.

Figure S5 (*Continued*)

C

Meta-analysis fixed-effects estimates (linear form) study omitted

Figure S5 The sensitivity analysis of pancreatic cancer risk associated with NR5A2 polymorphism.
Notes: (**A**) Heterozygous model (GA vs GG) for rs3790843 G>A; (**B**) recessive model (CC vs TT+CT) for rs3790844 T>C; (**C**) allele model (T vs C) for rs12029406 C>T.

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2. Hongwei T, Xiaoqun D, Manal H, et al. Body mass index and obesity- and diabetes-associated genotypes and risk for pancreatic cancer. *Cancer Epidemiol Biomarkers Prev*. 2011;20(5):779–792.
3. Cosmeri R, Daniele C, Nathalia G, et al. Pancreatic cancer susceptibility loci and their role in survival. *PLoS One*. 2011;6(11):e27921.
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