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Pancreatitis-Associated Genes and Pancreatic Cancer Risk

A Systematic Review and Meta-analysis

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Objective: The aim of this study was to evaluate the connection between pancreatic cancer (PC) and genetic variants associated with chronic pancreatitis via systematic review and meta-analysis.

Methods: The data search was performed in 3 major databases (PubMed, Embase, and Cochrane Library). The selected studies have looked into the presence of the pancreatitis-associated genes in patients with PC and in control subjects, the outcome being the frequency of the mutations in the 2 groups. For the binary outcomes, pooled odds ratio (OR) and 95% confidence interval (CI) were calculated.

Results: Ten articles proved to be eligible for the qualitative synthesis, and 8 articles were suitable for statistical analysis. Six case-control studies, comprising 929 PC cases and 1890 control subjects for serine protease inhibitor Kazal type 1 (*SPINK1*) mutations, and 5 case-control studies, comprising 1674 PC cases and 19,036 control subjects for *CFTR* mutations, were enrolled in our analysis. *SPINK1* mutations showed no association with PC (OR, 1.52; 95% CI, 0.67–3.45; $P = 0.315$), whereas mutations in *CFTR* modestly increased the risk of PC (OR, 1.41; 95% CI, 1.07–1.84; $P = 0.013$).

Conclusion: Our meta-analysis showed that mutations in *CFTR* modestly increase the risk of PC, whereas no association was found between *SPINK1* and PC.

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Pancreatic cancer (PC) is one of the most lethal and therapeutically resistant malignancies, with a grim prognosis that is related to the late clinical presentation and the rapid progression of the disease. Despite extensive research, the etiology and pathomechanism remain ambiguous. Both genetic and environmental factors play a role in the development and progression of PC.[1] A better understanding of the risk factors that are responsible for the development of PC is needed, not only to establish early detection strategies for high-risk population, but also to refine the understanding of the disease mechanism. Among environmental risk factors, cigarette smoking is dominant, causing approximately 20% of PC cases.[2]

The overwhelming majority of PC cases are thought to be sporadic; only up to 10% can be attributed to genetic factors.[3] Numerous studies have found a connection between chronic pancreatitis (CP) and PC. Over a period of 20 years, around 5% of patients with CP will develop PC.[4–9] The risk of developing PC seems to be higher in patients with an early-onset pancreatitis caused by genetic factors. Mutations in the CP-susceptibility genes, such as cationic trypsinogen (*PRSS1*),[10] serine protease inhibitor Kazal type 1 (*SPINK1*),[11,12] chymotrypsin C (*CTRC*),[13] or cystic fibrosis transmembrane conductance regulator (*CFTR*)[14] genes can determine hereditary pancreatitis (HP), idiopathic CP, and cystic fibrosis (CF), respectively. It has been established that mutations in these genes are related to trypsinogen activation and chloride and bicarbonate transport, and they cause CP.[15] In 2013, carboxypeptidase A1 (*CPA1*) was also identified as a pancreatitis susceptibility gene.[16] Moreover, *CEL-HYB*, a hybrid allele that arose from a crossover between the 3′ end of the carboxyl ester lipase (*CEL*) gene and the nearby *CEL* pseudogene (*CELP*), was recently identified as a risk factor for CP.[17]

Studies have shown that long-standing CP caused by mutations in these genes is a risk factor for developing PC. Specifically, the estimated accumulated risk of PC in patients with HP by the age of 70 years is close to 40%.[18] Cystic fibrosis is another early-onset form of CP with a genetic basis. Patients with CF are at increased risk of developing digestive tract cancers (~6 fold) and PC.[19,20] An increased risk of PC was also observed in patients with tropical pancreatitis, a form of idiopathic CP seen in tropical Asia and Africa.[5,21] The association between long-standing CP and cancer seems clear, 30 to 40 years of inflammation being required before an appreciable percentage of patients with CP develop PC.[3]

On the basis of the association between these genetic variants and CP on the one hand and between CP and PC on the other hand, a connection between pancreatitis-related genes and cancer

risk might be expected. Studies have been performed to assess the association between mutations in the pancreatitis-related genes and PC. However, the results were inconsistent or even contradictory, partially because of the possible small effect of these mutations on cancer risk and the relatively small sample size in each of the published studies. Therefore, we performed a systematic review and meta-analysis to further assess the possible connection between mutations in the pancreatitis-associated genes and the risk of PC.

Our study was performed using the PICO (population, intervention, comparison, outcome) format. The selected studies have looked into the presence of the pancreatitis-associated genes (P) in patients with PC (I) and in control subjects (C), the outcome (O) being the frequency of the mutations in the 2 (I and C) groups. The aim of our study was therefore to evaluate a potential association between these mutations and PC.

MATERIALS AND METHODS

Search Strategy and Study Selection

Our study was conducted following the principles of the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-analysis Protocol) statements.[22] A review protocol was registered for this meta-analysis (its PROSPERO registration no. CRD42017062449).

A systematic literature search was carried out by 2 investigators independently until March 2017, to screen for case-control studies characterizing the association between pancreatitis-associated genes mutations and PC risk. The data search was performed in 3 major databases: PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Embase (https://www.embase.com), and Cochrane Library (http://www.cochranelibrary.com). The search terms used were as follows: "pancreatic cancer" AND ("*PRSS1*" or "*SPINK1*" or "*CFTR*" or "*CTRC*" or "*CPA1*"or "*CEL*").

Our search was limited to human studies written in English. No other restrictions were applied in the search. In order to identify other potentially eligible publications, we also manually reviewed the references from primarily identified studies and review articles.

Inclusion and Exclusion Criteria

The studies enrolled in the meta-analysis were required to meet the following criteria: (1) they should focus on the association between pancreatitis-related genes and PC risk, (2) they should be designed as case-control studies, and (3) they should contain sufficient data for the estimation of odds ratio (OR) with a 95% confidence interval (CI). The exclusion criteria were: case-only studies, family studies, case reports, or reviews.

Data Extraction

Two reviewers independently performed data extraction, in accordance with the inclusion and exclusion criteria listed previously. Disagreements were resolved by reaching a consensus among all authors. For each study, we recorded the following information: name of first author, year of publication, study design, total number of PC cases and control subjects, and the number of cases and control subjects with mutations in the pancreatitis-associated genes. Different spreadsheets were designed for each gene (see Supplemental Digital Content 1, http://links.lww.com/MPA/A672, which contains raw data material).

Quality Assessment of the Included Studies

The Newcastle-Ottawa quality assessment scale (NOS) was used to evaluate the quality of each included study.[23] The Newcastle-Ottawa quality assessment scale assesses studies from the following 3 aspects: selection, comparability, and exposure. The score range of NOS is from 0 to 9, and studies with a score greater than 7 are assumed to be of high quality. The quality assessment was conducted by 2 investigators independently, and any disagreement between the investigators was resolved by a discussion with the third investigator.

Statistical Methods

The statistical methods of this study were reviewed by N.F. from the Institute of Bioanalysis, University of Pécs, Hungary. In our meta-analysis, we used the random-effect model by DerSimonian and Laird.[24] For the binary outcomes, pooled OR and 95% CI were calculated. Heterogeneity was tested using Cochrane Q and the I^2 statistics. The Q homogeneity test statistic exceeds the upper-tail critical value of χ^2 on $k-1$ degrees of freedom; $P < 0.05$ was considered suggestive of significant heterogeneity. The I^2 statistic represents the percentage of the total variability across studies, which is due to heterogeneity. I^2 values of 25%, 50%, and 75% corresponded to low, moderate, and high degrees of heterogeneity, based on *Cochrane Handbook*.[25]

The forest plot was used to represent the data. Publication bias was examined by visual inspection of funnel plots, in which the SE was plotted against the net change for each study. All statistical calculations were performed with STATA software version 11 (Stata Corporation, College Station, Tex).

RESULTS

Search Results and Study Characteristics

Through database search, we identified 683 potentially relevant records focusing on mutations in pancreatitis-associated genes and PC (321 articles in PubMed, 362 in Embase, and none in the Cochrane Library). From other sources (reference lists of screened studies), 13 additional records were obtained. After title and abstract screening and removing duplicates, 67 records remained for detailed assessment of eligibility. Altogether, 10 articles[1,26–34] proved to be eligible for our systematic review and meta-analysis. Ten articles were included in the qualitative synthesis, and 8 articles were suitable for statistical analysis (quantitative synthesis (Fig. 1).

The eligible case-control studies were published between 2002 and 2017. A total of 6 studies, comprising 929 PC cases and 1890 control subjects for *SPINK1* mutations, and 5 case-control studies, comprising 1674 PC cases and 19,036 control subjects for *CFTR* mutations, were enrolled in our analysis. We found only 2 articles on *CEL*, 1 on *CTRC*, 1 on *PRSS1*, and none on *CPA1* mutations.

Regarding control group sources, 8 studies applied population-based control. In 1 study,[27] the control group included patients who would not be expected to have an increased prevalence of pancreatitis-associated genes alterations. These patients had chronic cholecystitis and colorectal carcinoma. One of the studies[33] used both population and hospital-based control subjects. The baseline characteristics of the included studies are summarized in Table 1.

The average NOS score of the included studies was 6.5 (range, 6–8), indicating that all enrolled articles were of relatively high quality (Table 1).

CFTR Mutations and PC Susceptibility

Overall, our meta-analysis yielded a positive association of PC risk with *CFTR* carrier status (OR, 1.41; 95% CI, 1.07–1.84;

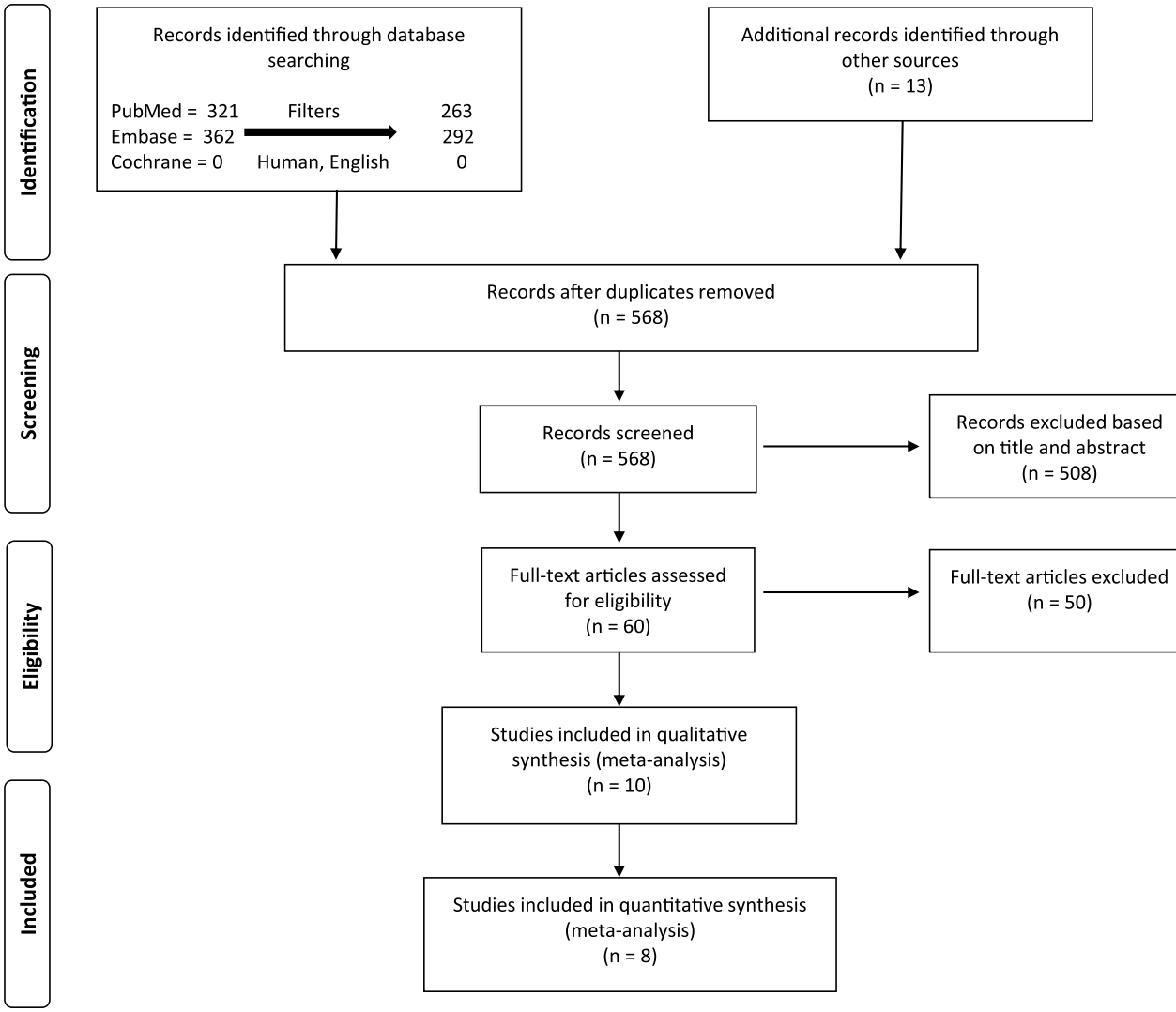

FIGURE 1. Flowchart of the systematic literature search.

$P = 0.013$; Fig. 2). There was no obvious evidence of between-study heterogeneity ($I^2 = 9.6\%$, $df = 4$, $P = 0.351$).

Thirteen different *CFTR* mutations were analyzed, and their frequencies in PC patients and control subjects are compared in Table 2. Our results showed a statistically significant association of 4 *CFTR* mutations and PC risk (*del508F*: OR, 0.64 [95% CI, 1.17–2.31; $P = 0.004$]; *W1282X*: OR, 13.64 [95% CI, 4.29–43.39; $P < 0.01$]; *ΔI507*: OR, 42.19 [95% CI, 1.72–1036.47; $P = 0.022$]; *S549R*: OR, 42.19 [95% CI, 1.72–1036.47; $P = 0.022$]). For *F1052V* and *D1152H* variants, OR could not be calculated because the mutations were present neither in PC patients nor in control subjects. Other *CFTR* mutations did not seem to significantly increase the risk of PC (Fig. 3).

SPINK1 Mutations and PC Risk

Regarding *SPINK1* mutations, no significant association with PC risk was found (OR, 1.52; 95% CI, 0.67–3.45, $P = 0.315$; Fig. 4). No obvious between-study heterogeneity was detected ($I^2 = 47.6\%$, $df = 5$, $P = 0.089$). Three different *SPINK1* polymorphisms were analyzed, and their prevalence was similar among PC patients and control subjects (Table 3). Our results did not show statistically significant association between any of the *SPINK1* mutations and PC (*N34S*: OR, 1.48 [95% CI, 0.66–3.31; $P = 0.342$]; *P55S*: OR, 1.41 [95% CI, 0.24–8.26; $P = 0.706$]; *c.194+2T>C*: OR, 5.61 [95% CI, 0.58–54.23; $P = 0.136$]; Fig. 5).

Publication Bias

Funnel plots were used to evaluate the potential publication bias. A visual inspection of the funnel plots revealed no apparent asymmetry, and these results suggest that there was no significant publication bias in the present meta-analysis (see Supplemental Digital Content 2, http://links.lww.com/MPA/A673, which represents the funnel plot of publication biases of the studies included in Fig. 2, and Supplemental Digital Content 3, http://links.lww.com/MPA/A673, which represents the funnel plot of publication biases of the studies included in Fig. 4).

DISCUSSION

The impact of pancreatitis susceptibility gene alterations on PC is poorly understood. Most experts agree that patients with *PRSS1*-associated CP should be carefully screened for PC[18,36];

TABLE 1. Baseline Characteristics of the Studies Included in the Meta-analysis and Systematic Review

Author, Year	Investigated Gene	Group	Sample Size	Control Source	Sex, F/M, n	Age*, y	NOS[23]
Schubert et al,[26] 2014	*SPINK1, PRSS1*	PC	121	Population based	71/50	38–86	6
	CFTR	C	130		40/90	21–45	
	CTRC						
Matsubayashi et al,[27] 2003	*SPINK1*	PC	236	Hospital based	nd	nd	6
	CFTR	C	177				
Piepoli et al,[1] 2006	*SPINK1*	PC	61	Population based	30/31	63 (10)	7
	CFTR	C	105		nd	39 (9)	
Teich et al,[28] 2003	*SPINK1*	PC	159	Population based	76/83	36–84	7
		C	492		nd	nd	
Lempinen et al,[29] 2005	*SPINK1*	PC	188	Population based	102/86	23–97	7
		C	459		367/92	19–66	
Shimosegawa et al,[30] 2009	*SPINK1*	PC	164	Population based	nd	nd	5
		C	527				
McWilliams et al,[32] 2010	*CFTR*	PC	949	Population based	399/550	28–91	6
		C	13,340		12,840/534	18–81	
McWilliams et al,[31] 2005	*CFTR*	PC	166	Population based	nd	nd	6
		C	5349		nd	nd	
Shindo et al,[33] 2017	*CEL*	PC	850	Population/hospital based	397/453	65 (10.6)	8
		C	976		nd	nd	
Dalva et al,[35] 2017/German cohort	*CEL*	PC	265	Population based	nd	nd	7
		C	502		nd	nd	
Dalva et al,[35] 2017/Norwegian cohort	*CEL*	PC	197	Population based	nd	nd	7
		C	380		nd	nd	

*Age shown as range or median (SD).

C indicates control; F, female; M, male; nd, no data.

on the other hand, the risk of PC among patients with other genetically associated pancreatitis is less clear. When the alterations of these genes were investigated in patients with PC, the results have been inconclusive. To the best of our knowledge, this is the first meta-analysis evaluating the association between genetic variants associated with CP and PC. As a whole, we found that mutations

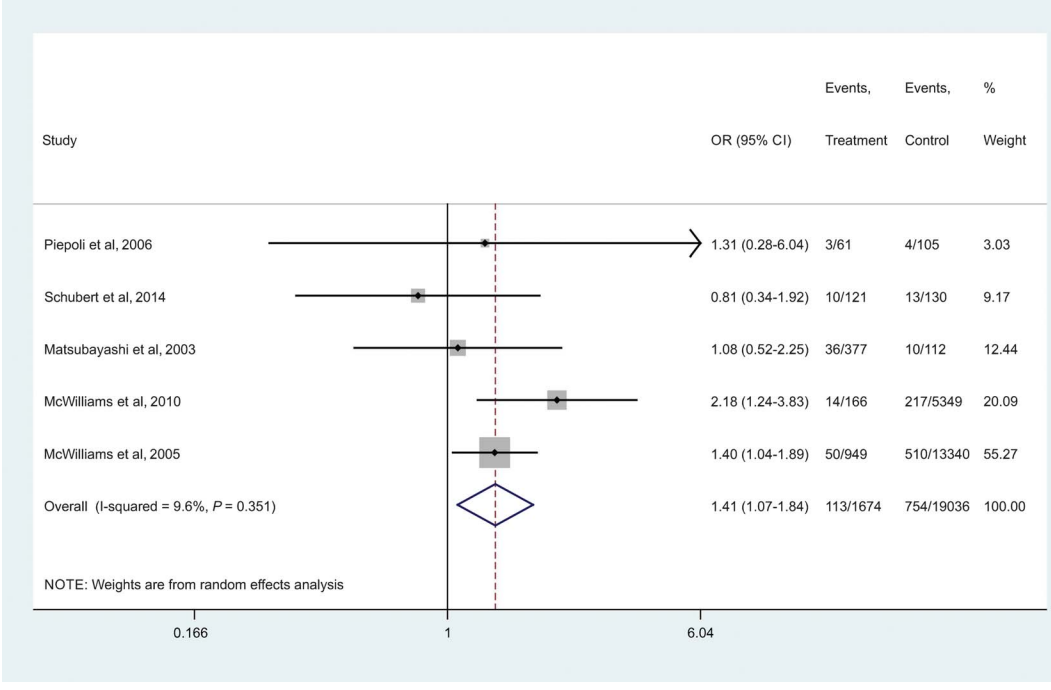

FIGURE 2. Forest plot of studies evaluating the association between PC risk and *CFTR* carrier status.

TABLE 2. *CFTR* Mutation Frequencies in PC Cases and Control Subjects

			CFTR Variants, n											
Author, Year	**Group**	**N**	***5t***	***ΔF508***	***R553X***	***F1052V***	***D1152H***	***N1303K***	***R117H***	***G551D***	***W1282X***	***R347P***	***S549R***	***ΔI507***	***R347H***
Schubert et al,[26] 2014	PC	121	8	2	0	0	0	0	0						
	C	130	7	2	1	0	0	1	2						
Matsubayashi et al,[27] 2003	PC	377	36												
	C	112	10												
Piepoli et al,[1] 2006	PC	61		3											
	C	105		4											
McWilliams et al,[32] 2010	PC	959						1	5	1	5	1	1	1	
	C	13,340						8	71	11	5	2	0	0	
McWilliams et al,[31] 2005	PC	166						1	1	0	0				0
	C	5349						3	28	6	1				1

C indicates control.

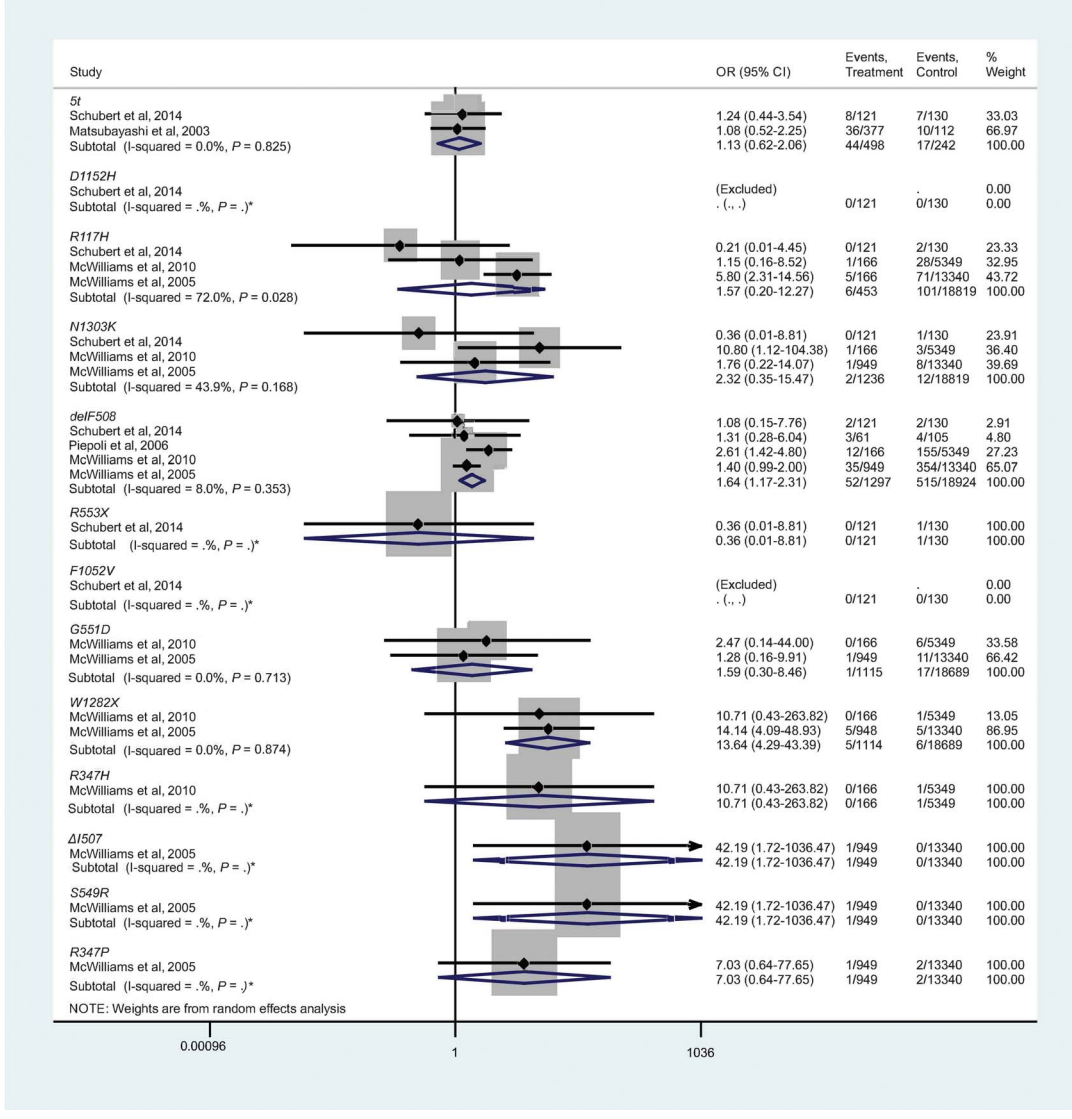

FIGURE 3. Forest plot of studies evaluating the association between different *CFTR* genetic variants and susceptibility of PC. *Not enough data to calculate I^2 and *P* values.

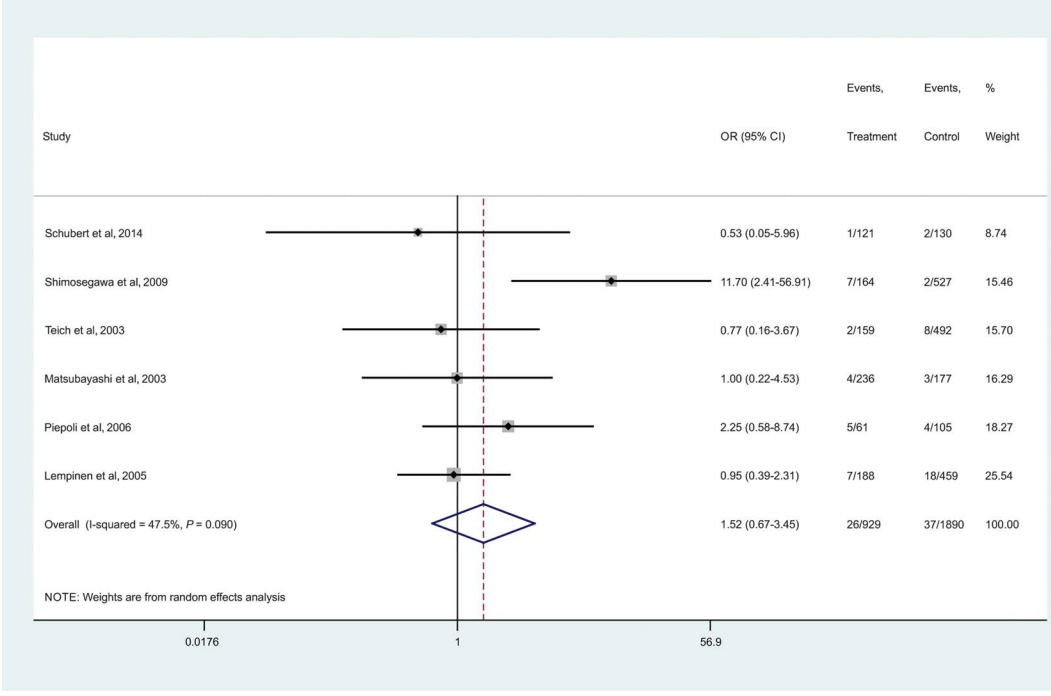

FIGURE 4. Forest plot of studies evaluating the association between *SPINK1* carrier status and PC risk.

in the *CFTR* gene are associated with a modest increase in the risk of PC, whereas no association was found between *SPINK1* and PC. Regarding the other pancreatitis-associated genes, there were not enough studies assessing their connection with PC, and consequently the available data were not suitable for meta-analysis.

Mutations in the *SPINK1* gene were identified as a genetic risk factor for CP. A recent meta-analysis by Liu et al[37] indicated a strong association between *SPINK1* variants, especially N34S, and pancreatitis. *SPINK1* protects the pancreas against inappropriate premature intracellular activation of trypsinogen. Numerous variants of the *SPINK1* gene have been described, *N34S* and *P55S* mutations being the most common ones. These mutations reduce the antiproteolytic activity of *SPINK1*, leading to premature pancreatic enzyme activation and subsequent pancreatic inflammation.[38] Based on the association between this mutation and CP and the fact that continuous inflammatory stimulation may lead to the development of PC, an association between *SPINK1* mutations and cancer might be expected. However, our meta-analysis shows that the prevalence of the *SPINK1* mutations in patients with pancreatic carcinomas was not higher than that of control groups. Therefore, our data suggest that *SPINK1* mutations are not associated with an increased risk of developing PC. Most studies included in our meta-analysis focused on the analysis of the following mutations in the *SPINK1* gene: *N34S*, *P55S*, and *c.194+2T>C*. However, there was no significant difference in risk based on the type of mutation. Although our results indicate that there is no direct association between *SPINK1* mutations and the risk

TABLE 3. *SPINK1* Variant Frequencies in PC Cases and Control Subjects

			***SPINK1* Variants, n**		
Author, Year	**Group**	**Sample**	***N34S***	***P55S***	***c.194+2T>C***
Schubert et al,[26] 2014	PC	121	0	0	1
	C	130	1	1	0
Matsubayashi et al,[27] 2003	PC	377	4		
	C	112	3		
Piepoli et al,[1] 2006	PC	61	1	4	
	C	105	2	2	
Teich et al,[28] 2003	PC	159	2		
	C	492	8		
Lempinen et al,[29] 2005	PC	188	7	0	
	C	459	12	6	
Shimosegawa et al,[30] 2009	PC	164	6	1	1
	C	527	2	0	0

C indicates control.

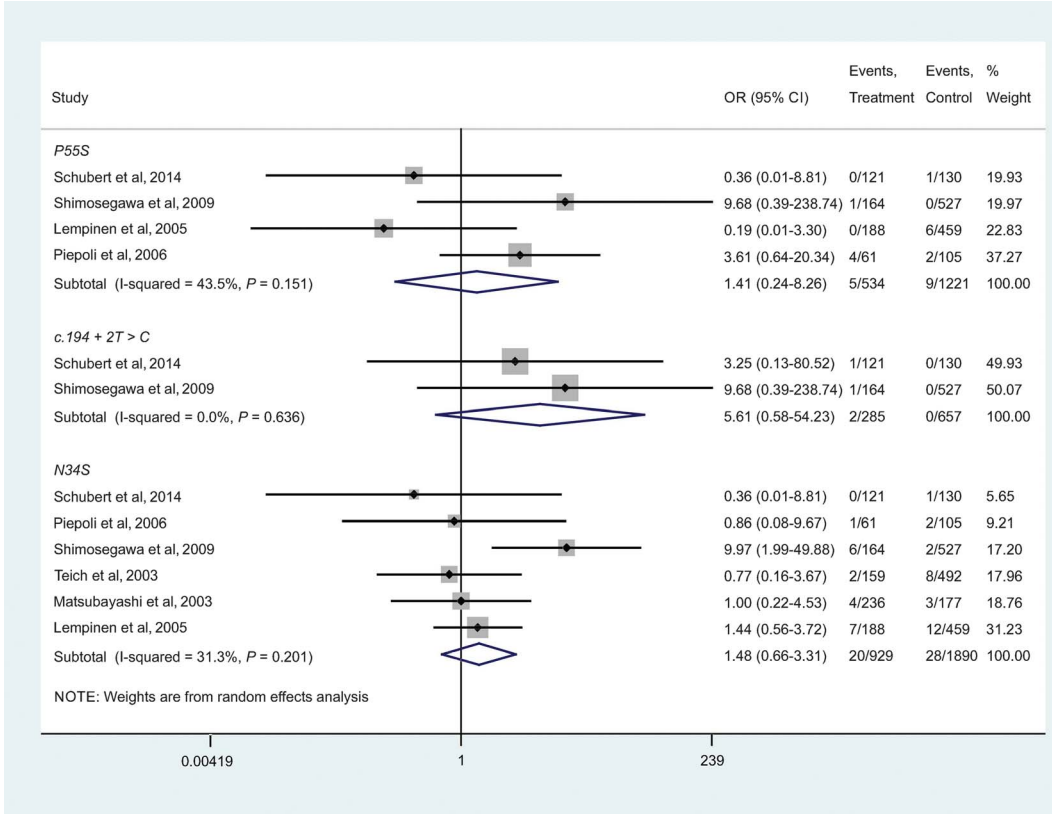

FIGURE 5. Forest plot of studies evaluating the association between different *SPINK1* variants and PC.

of PC, we cannot exclude the possibility that among the carriers of this mutation, there could be an increased risk of developing PC, but this risk is more likely to be caused by the ability of this mutation to determine CP rather than a direct cancer-promoting effect.

The *CFTR* protein is essential for the normal bicarbonate secretion by pancreatic duct cells, conducting both chloride and bicarbonate. Mutations in the *CFTR* genes have been found to be associated with CP.[39] To date, more than 2000 *CFTR* mutations have been described. The 2 most frequent mutations of *CFTR* are the *del508F* mutation, a CF-causing variant and the *5T* polymorphism, which has varying clinical consequences. In our study, we analyzed the connection between 13 disease-associated mutations in *CFTR* gene and PC susceptibility. Our results showed that carrying a germline mutation in *CFTR* modestly increases the risk of pancreatic adenocarcinoma. We found a positive association between PC and 4 of the 13 *CFTR* mutations that were analyzed (*del508F*, *W1282X*, *ΔI507*, *S549R*), all of them being CF-causing variants. The association of the other *CFTR* variants with PC was not statistically significant. Mutation carriers also appear to be diagnosed at a younger age than noncarriers, especially among smokers.[32]

There are some potential mechanisms for cancer development in *CFTR* mutation carriers. First, mutations in the *CFTR* gene lead to CP, and the long-standing inflammation increases the risk of neoplastic transformation. Second, the tumor-suppressing role of *CFTR* and its involvement in regulation of miR-193b in prostate cancer development have been described.[40] Third, the cells lacking functioning *CFTR* have an inadequate control of apoptosis because of a defective regulation of the cell's glutathione concentration.[41] Moreover, patients with *CFTR* mutations and consequent exocrine pancreatic insufficiency may develop deficiencies of selenium and vitamin E, which are antioxidants and are presumed to offer protection from cancer.[42]

Regarding *PRSS1* gene mutations, we found only 1 study that met our inclusion criteria[26]; therefore, a meta-analysis could not be performed. The results of that study indicate that *PRSS1* mutations do not confer an elevated risk of PC. Clearly, the data basis for the estimation of this association is small. Moreover, although *PRSS1* is neither an oncogene, nor a tumor-suppressor gene, it is involved in repairing or maintaining the self-stability of cells,[43] and a mutation in this gene can increase the risk of cancer development. The gain-of-function mutations of the *PRSS1* gene can cause HP. Patients with HP show an exceptionally high risk of PC that can approach 40% by the age of 70 years.[18] Taking everything into consideration, further studies are necessary to investigate the association between PC risk and *PRSS1* mutations.

Similarly, the same study investigated the connection between *CTRC* gene mutations and cancer risk.[26] No additional studies on this topic were found. Loss of function or missense *CTRC* mutations have also been reported to be associated with CP, but do not seem to increase the risk of PC.[26]

In 2013, *CPA1* was also identified as a pancreatitis susceptibility gene.[16] Recently, preliminary evidence was found about the contribution of *CPA1* gene to PC risk.[44] Deleterious mutations in *CPA1* were identified in patients with familial forms of PC. However, the data available were insufficient for meta-analysis.

Recently, copy number variants (CNVs) of the human *CEL* gene, including a recombined deletion allele (*CEL-HYB*) and a duplication allele *(CEL-DUP*),[17] were also identified as a genetic risk factor for CP. We found 2 studies that examined whether *CEL* CNVs affect the risk of developing PC.[33,35] Both were unable to

reveal an association between the CEL CNVs and PC. The frequency of the *CEL-HYB* allele is low, and its associated CP risk is intermediate. Therefore, it may not be surprising that *CEL-HYB* is rarely detected in patients with PC. Nevertheless, this allele could determine an increased risk in those carriers that develop CP, especially if the onset of pancreatitis is in the early period of life. Moreover, *CEL* is a highly polymorphic gene, and yet uncharacterized CNVs are very likely to exist. It is consequently too early to rule out that genetic variants of *CEL* could play a role in PC. Additional epidemiologic studies in large populations may be able to clarify this issue.

Only few studies provided data regarding underlying CP in patients with PC.[26,28–32] Regarding *SPINK1* variants, only 5 of 17 PC patients had an antecedent history of pancreatitis, and 4 of 74 *CFTR* carriers with PC had underlying CP. In the other cases, either the pancreatitis was subclinical, or the presence of these genetic variants may increase the risk of PC through a mechanism independent of CP or inflammation.

Several limitations of our study should be noted, which are a direct consequence of the limited literature on this topic. First, in order to drive a more precise estimation of the association between these genes and cancer risk, studies including PC patients with underlying CP should have been considered, but their number was limited and not suitable for meta-analysis. Second, our results were based on unadjusted estimates, because the majority of the included studies failed to report the baseline characteristics of the individuals (such as age, sex, smoking status). Third, all included studies were published in English; therefore, some qualified articles in other languages may have been missed. Fourth, the relationship between a certain gene polymorphisms and cancer risk could be affected by gene-gene or gene-environment interactions. It is possible, that a specific polymorphism may be associated with cancer susceptibility, but because of interactions with multiple genetic and environmental factors, the association would no longer be observed. We could not assess these interactions because of lacking data. Furthermore, we found that mutations in the *CFTR* gene modestly increase the risk of PC, but this could be due to the population-based control, which may have resulted in a positive association by random chance. Given these limitations, we should interpret the current results with caution.

Despite the limitations, the statistical power of our meta-analysis significantly increased the strength of evidence in this topic, based on substantial number of cases and control subjects from different studies. Our study is the first meta-analysis on this topic, and it offers a better understanding of the genetic risk factors that are responsible for the development of PC.

CONCLUSIONS

The present meta-analysis shows that mutations in *CFTR* gene are associated with a modest increase in the risk of PC, whereas no association is found between *SPINK1* and PC. Further well-designed studies are needed to verify the results of the present meta-analysis, which can be translated into clinical recommendations, having important implications for the development of chemoprevention and early detection strategies.

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