CASE CONTROL STUDY

Case-control study of diabetes-related genetic variants and pancreatic cancer risk in Japan

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Abstract

AIM: To examine whether diabetes-related genetic variants are associated with pancreatic cancer risk.

METHODS: We genotyped 7 single-nucleotide polymorphisms (SNPs) in *PPARG2* (rs1801282), *ADIPOQ* (rs1501299), *ADRB3* (rs4994), *KCNQ*1 (rs2237895), *KCNJ11* (rs5219), *TCF7L2* (rs7903146), and *CDKAL1* (rs2206734), and examined their associations with pancreatic cancer risk in a multi-institute case-control study including 360 cases and 400 controls in Japan. A self-administered questionnaire was used to collect detailed information on lifestyle factors. Genotyping was performed using Fluidigm SNPtype assays. Unconditional logistic regression methods were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between these diabetes-associated variants and pancreatic cancer risk.

RESULTS: With the exception of rs1501299 in the

ADIPOQ gene (*P* = 0.09), no apparent differences in genotype frequencies were observed between cases and controls. Rs1501299 in the *ADPIOQ* gene was positively associated with pancreatic cancer risk; compared with individuals with the AA genotype, the age- and sex-adjusted OR was 1.79 (95%CI: 0.98-3.25) among those with the AC genotype and 1.86 (95%CI: 1.03-3.38) among those with the CC genotype. The ORs remained similar after additional adjustment for body mass index and cigarette smoking. In contrast, rs2237895 in the *KCNQ1* gene was inversely related to pancreatic cancer risk, with a multivariable-adjusted OR of 0.62 (0.37-1.04) among individuals with the CC genotype compared with the AA genotype. No significant associations were noted for other 5 SNPs.

CONCLUSION: Our case-control study indicates that rs1501299 in the ADIPOQ gene may be associated with pancreatic cancer risk. These findings should be replicated in additional studies.

Key words: Single-nucleotide polymorphisms; Pancreatic cancer; Risk; Case-control study; Odds ratio

Core tip: Although it is likely that a common genetic background predisposes individuals to developing both diabetes and pancreatic cancer, very few molecular epidemiologic studies have addressed this issue. We therefore genotyped 7 diabetes-related genetic variants and found that rs1501299 in the ADIPOQ gene may be associated with pancreatic cancer risk. The role of adiponectin variants needs further study.

INTRODUCTION

The etiology of sporadic pancreatic cancer remains largely unknown. Epidemiologic studies have consistently shown that pancreatic cancer is positively associated with cigarette smoking and long-standing diabetes[1,2]. A 2005 meta-analysis reported that the risk for pancreatic cancer is 82% higher among diabetics compared with those without diabetes[3], though it is unclear which factors underlying diabetes are associated with pancreatic cancer. Most epidemiological studies have been limited by self-reporting of diabetes and by the lack of objective biomarkers, such as fasting plasma glucose or insulin levels, to address the temporal relationship between diabetes and pancreatic cancer. There is increasing evidence from clinical studies that pancreatic cancer induces new-onset diabetes[4,5]. The evidence available thus far strongly suggests that the relationship between diabetes and pancreatic cancer is bi-directional.

Given the well-recognized, positive association between type 2 diabetes and pancreatic cancer risk in epidemiological studies, it may be interesting to examine whether diabetes-related genetic variants may also be associated with pancreatic cancer risk. Genome-wide association studies (GWAS) have reported that at least 30 loci are associated with susceptibility to diabetes in various populations, with the majority originating from individuals of European descent[6]. Because of the potential differences in fat distribution and genetic background between Asian and Western populations[7,8], we focused on diabetes-related genetic variants reported in studies of Japanese populations, and variants that were first reported in GWAS of other populations and then replicated in Japanese populations. Among the 7 diabetes susceptibility genes we chose for the present study, *PPARG2*, *ADIPOQ*, and *ADRB3* have been shown to be closely associated with diabetes risk in Japanese subjects[9]; *KCNQ1* was reported as a diabetes susceptibility gene simultaneously by 2 independent Japanese research groups in 2008[10,11]; *KCN11*, *TCF7L2*, and *CDKAL1* were also reported to be associated with diabetes susceptibility in GWAS of Japanese subjects[12,13].

Although it is likely that a common genetic background predisposes individuals to developing both diabetes and pancreatic cancer, very few molecular epidemiologic studies have addressed this issue. We hypothesized that diabetes susceptibility genetic variants may be associated with an increased risk of pancreatic cancer in Japanese subjects. We therefore genotyped 7 single-nucleotide polymorphisms (SNPs) in *PPARG2* (rs1801282), *ADIPOQ* (rs1501299), *ADRB3* (rs4994), *KCNQ1* (rs2237895), *KCNJ11* (rs5219), *TCF7L2* (rs7903146), and *CDKAL1* (rs2206734) and examined their associations with pancreatic cancer risk in a multi-institute, case-control study in Japan.

MATERIALS AND METHODS

Study subjects

The purpose of our case-control study was to evaluate the role of genetic polymorphisms and gene-environment interactions in the development of pancreatic cancer in Japanese subjects. The details of the study design have been described elsewhere[14]. Briefly, cases were defined as patients who were newly diagnosed with pancreatic ductal adenocarcinoma at five participating hospitals from April 1, 2010, through May 15, 2012. A diagnosis was made according to imaging modalities and further confirmed by pathology reports. Pathologically confirmed cases represented approximately 90% of all cases in this study. During the same time period, we recruited the majority of control subjects from in-

Table 2 Selected characteristics of cases and controls *n* (%)		
	Cases *n* = 360	Controls *n* = 400
Age, mean ± SD	67.8 ± 8.8	64.8 ± 9.5
Sex		
Male	215 (59.7)	226 (56.5)
Female	145 (40.3)	174 (43.5)
BMI, mean ± SD	22.9 ± 3.3	22.8 ± 3.2
History of diabetes		
Yes	87 (24.1)	35 (8.7)
No	269 (74.7)	362 (90.5)
Cigarette smoking		
Ever	215 (59.7)	198 (49.5)
Never	145 (40.2)	202 (50.5)
Age upon starting smoking (mean ± SD)	21.8 ± 4.8	20.5 ± 4.5
Number of cigarettes smoked per day (mean ± SD)	20.3 ± 9.0	16.2 ± 9.2

BMI: Body mass index.

Table 2 Single-nucleotide polymorphisms profile				
Rs number	Gene	Chromosome location	Risk allele[1]	Alternative allele
rs1801282	*PPARG2*	3p25	C	G
rs1501299	*ADIPOQ*	3q27	C	A
rs4994	*ADRB3*	8p12	C	T
rs2237895	*KCNQ1*	11p15	C	A
rs5219	*KCNJ11*	11q23	T	C
rs7903146	*TCF7L2*	10q25	T	C
rs2206734	*CDKAL1*	6p22	A	G

[1]Based on the odds ratios reported for the association between T2D risk allele and T2D risk in previous studies.

patients and outpatients as well as from individuals who underwent medical checkups at one of the participating hospitals. None of the control subjects had a history of cancer. The diagnoses for hospital control subjects included a variety of diseases, such as anemia, gastric ulcers, and irritable bowel syndrome. The response rate was 85% (441/516) for cases and 98% (525/534) for control subjects as of July 1, 2012. The control subjects were frequency matched to the case patients on sex and age (within 10-year categories). As a result, 360 case patients and 400 control subjects were included in the present analysis.

All the study subjects provided written informed consent. Our study was approved by the Ethics Board of Aichi Medical University and by all the participating hospitals.

Data collection

Using a self-administered questionnaire, we collected detailed information on demographic characteristics, medical history, and lifestyle factors. In addition to the questionnaire survey, we obtained a 7-mL venous blood sample from all consenting participants. Genomic DNA was extracted from peripheral lymphocytes and subsequently stored at -30 ℃ until analysis.

Genotyping assays

Genotyping was performed using Fluidigm 192.24 Dynamic Array with BioMark HD Systems and EP1 (Fluidigm Corp., CA). We applied SNPtype assay (Fluidigm Corp., CA) which employs allele-specifically designed fluorescences (FAM or VIC) primers and a common reverse primer. We analyzed the data by the BioMark SNP Genotyping Analysis software to obtain genotype calls. The software defined genotype of each sample based on the relative intensities of fluorescences. The laboratory staff members were blinded to case or control status. Four quality control samples were included in each assay, and the successful genotyping rate was 100%.

Statistical analysis

A χ^2 test was used to test genotype frequencies in control subjects for Hardy-Weinberg equilibrium (HWE) by comparing the observed genotype frequencies with those expected under HWE. The differences in genotype frequencies between cases and controls were also tested using a χ^2 test. Because the biological function of most SNPs has not been clearly defined, a co-dominant genomic model was assumed for SNP effects. We used unconditional logistic regression methods to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between diabetes-associated variants and pancreatic cancer risk. All analyses were adjusted for age (continuous), sex (male or female), BMI (< 20, 20-22.4, 22.5-24.9, or $\geq$ 25.0), and cigarette smoking (current, former, or never smokers). ORs were also estimated for the risk allele on the basis of a log-additive model.

All *P* values were two-sided, with *P* < 0.05 indicating statistical significance. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for the R program (The R Foundation for Statistical Computing). More precisely, EZR is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

RESULTS

The distribution of genotypes for all SNPs among control subjects did not deviate from HWE. Table 1 shows the selected characteristics of cases and controls. The mean BMI was similar between cases and controls. The number of individuals who had a history of diabetes was 87 (24.1%) in cases and 35 (8.7%) in controls. The OR was 2.95 (95%CI: 1.90-4.57) for those who had a history of diabetes. Individuals who had a BMI of 30 or greater had a 1.21-fold increased risk; however, the association was not statistically significant. The number of ever smokers (including current and former smokers) was 215 (59.7%) in cases and 198 (49.5%) in controls. The SNP profile is summarized in Table 2.

Table 3 shows the associations of pancreatic cancer with individual SNPs in the following genes: *PPARG2*

Table 3 Associations between diabetes-associated single-nucleotide polymorphisms and pancreatic cancer risk

Gene	SNP	Genotype	Case, *n*	Control, *n*	Age- and sex-adjusted OR (95%CI)	[1]Multivariable-adjusted OR (95%CI)
PPARG2	rs1801282	GG + CG	26	27	1.00	1.00
		CC	334	373	0.83 (0.47-1.46)	0.77 (0.43-1.38)
ADIPOQ	rs1501299	AA	19	38	1.00	1.00
		AC	155	167	1.79 (0.98-3.25)	1.71 (0.93-3.15)
		CC	186	195	1.86 (1.03-3.38)	1.85 (1.01-3.39)
CDKAL1	rs2206734	GG	114	138	1.00	1.00
		AG	184	195	1.15 (0.83-1.59)	1.18 (0.85-1.64)
		AA	62	67	1.16 (0.75-1.79)	1.21 (0.78-1.89)
ADRB3	rs4994	TT	228	255	1.00	1.00
		CT	114	131	0.92 (0.67-1.25)	0.88 (0.64-1.21)
		CC	18	14	1.37 (0.66-2.83)	1.36 (0.65-2.87)
KCNQ1	rs2237895	AA	153	156	1.00	1.00
		AC	175	193	0.95 (0.70-1.29)	0.92 (0.67-1.26)
		CC	32	51	0.62 (0.37-1.02)	0.62 (0.37-1.04)
KCNJ11	rs5219	CC	150	159	1.00	1.00
		CT	157	192	0.87(0.64-1.18)	0.90 (0.66-1.24)
		TT	53	49	1.14 (0.72-1.79)	1.19 (0.75-1.90)
TCF7L2	rs7903146	CC	354	394	1.00	1.00
		CT + TT	6	6	1.20 (0.38-3.83)	1.16 (0.36-3.72)

[1]Adjusted for age, sex, body mass index, and cigarette smoking.

(rs1801282), *ADIPOQ* (rs1501299), *ADRB3* (rs4994), *KCNQ1* (rs2237895), *KCNJ11* (rs5219), *TCF7L2* (rs7903146), and *CDKAL1* (rs2206734). With the exception of rs1501299 in the *ADIPOQ* gene ($P = 0.09$), no apparent differences in genotype frequencies were observed between cases and controls. Rs1501299 in the *ADPOQ* gene was positively associated with pancreatic cancer risk; the age- and sex-adjusted OR was 1.79 (95%CI: 0.98-3.25) among those with the AC genotype and 1.86 (95%CI: 1.03-3.38) among those with the CC genotype when compared with individuals with the AA genotype. The ORs remained similar after additional adjustment for cigarette smoking and BMI. Under the log-additive model, each additional copy of risk allele C was associated with a 1.2-fold increased risk of pancreatic cancer (OR = 1.22, 95%CI: 0.96-1.55). In contrast, rs2237895 in the *KCNQ1* gene was inversely related to pancreatic cancer risk, with a multivariable-adjusted OR of 0.62 (0.37-1.04) among individuals with the CC genotype compared with those with the AA genotype. No significant associations were noted for the other 5 SNPs.

DISCUSSION

In this case-control study, we genotyped 7 diabetes-associated genetic polymorphisms, and found that 2 variants in the *ADIPOQ* and *KCNQ1* genes were associated with pancreatic cancer risk in Japanese subjects. The risk variant in the *ADIPOQ* gene had a 1.9-fold increased risk, whereas the risk variant in the *KCNQ1* gene was inversely associated with risk.

Studies examining the association between diabetes-related genetic variants and pancreatic cancer risk were very limited, and the results were inconsistent. In a case-control study examining 15 SNPs in several obesity- and diabetes-related genes, two *FTO* gene variants (rs8050136 and rs9939609) and one *ADIPOQ* gene variant (rs17366743) were positively associated with pancreatic cancer risk; however, these associations were observed only in individuals who were overweight[15].

Of the 37 diabetes risk alleles examined by Pierce *et al*[16], only two SNPs (rs8050136 in *FTO* and rs1387153 in *MTNR1B*) showed significant positive associations with pancreatic cancer risk. However, *ADIPOQ* gene variants were not included in their analyses. We found that rs1501299 in the *ADIPOQ* gene had a positive association with pancreatic cancer risk, with the risk variant CC genotype conferring an approximate 1.9-fold increased risk compared with the AA genotype. The precise mechanism linking this SNP to pancreatic cancer risk is not clear. Adiponectin, which is secreted by adipose tissue, acts as an endogenous insulin-sensitizing hormone[17] and activates intracellular signaling pathways, including AMPK, PPARα, and NF-κB, by binding to two receptors, AdipoR1 and AdipoR2[17]. AdipoR1 has been reported to be upregulated in pancreatic cancer[18]. The adiponectin gene is located on chromosome 3q26, a region associated with susceptibility to the development of type 2 diabetes[19]. Rs1501299 in the *ADIPOQ* gene has been shown to be correlated with adiponectin levels, with the CC genotype exhibiting decreased levels of adiponectin compared with the AA genotype[9,20], Low adiponectin concentrations contribute to insulin resistance, type 2 diabetes, and atherosclerosis[21] as well as obesity-related cancers, including breast and colorectal cancers[22,23]. A prospective study showed that low plasma adiponectin levels are associated with an increased risk of pancreatic cancer, independent of other markers of insulin resistance[24]. Given the essential role of adiponectin in insulin resistance and the strong evidence supporting the positive association of pancreatic cancer with obesity, insulin resistance, and hyperinsulinemia in both

epidemiological and mechanistic studies, it is likely that genetic variations in the adiponectin pathway may affect pancreatic cancer risk through their effects on circulating adiponectin.

KCNQ1 (potassium voltage-gated channel KQT-like subfamily, member 1) encodes the pore-forming subunit of a voltage-gated K+ channel (KvLQT1) and plays a key role in the repolarization of cardiac action potential as a water and salt transporter in epithelial tissues[25]. *KCNQ1* is also expressed in pancreatic islets[26], and a blockade of the channel with the *KCNQ1* inhibitor 293B stimulated insulin secretion[27]. To date, variants in the *KCNQ1* gene exert the greatest effects on the risk of type 2 diabetes in Asians[28]. Of the several SNPs in the *KCNQ1* gene that are associated with increased type 2 diabetes risk in Asians[10,11], we selected rs2237895 because this SNP was reported to be significantly associated with diabetes risk in both GWAS of Japanese people. Furthermore, in a previous study examining the effects of 4 SNPs in the *KCNQ1* gene (rs2237892, rs2283228, rs2237895, and rs2237897) on serum insulin levels following an oral glucose tolerance test in approximately 6000 Scandinavian individuals, only the C risk allele of rs2237895 was associated with reduced insulin release[29]. A 2012 meta-analysis confirmed that the C risk allele of rs2237895 in the *KCNQ1* gene increases the risk of diabetes by 32%[30]. However, we found that the C risk allele of rs2237895 was associated with a decreased risk of pancreatic cancer, which is unexpected and contrary to our hypothesis. This finding may be due to chance, but the mechanisms underlying this inverse association should be explored in further studies.

Diabetes is a complex disease, and susceptibility is determined by both genetic and environmental factors. Additionally, pancreatic cancer develops only in a subset of diabetics. Thus, these factors led us to postulate that certain diabetes-predisposing variants may be associated with a decreased risk of pancreatic cancer. A nested case-control study offered supporting evidence that circulating markers of peripheral insulin resistance, rather than pancreatic β-cell dysfunction, were independently associated with pancreatic cancer risk[31]. This finding, together with our observation of the positive association between rs1501299 in the *ADIPOQ* gene and pancreatic cancer risk, indicates that genetic variations influencing insulin resistance and their impact on circulating biomarkers are closely associated with pancreatic cancer risk.

No significant differences were observed in the genotype distributions between cases and controls in this study, with the exception of rs1501299 in the *ADIPOQ* gene. Other than SNPs in the *ADIPOQ* and *KCNQ1* genes, none of the 5 SNPs we genotyped were associated with pancreatic cancer risk. Among the genes examined in this study, *TCF7L2*, the most significant diabetes-related gene in Western populations, did not show any significant associations in this study. One possible reason for this result is the difference in the minor allele frequency. The very low frequency of *TCF7L2* risk genotypes in

this study might make the detection of significant associations difficult. The null association for these SNPs suggests that other causal SNPs in these genes may be involved in pancreatic cancer susceptibility, and further studies are warranted to identify novel risk variants.

Our findings should be interpreted cautiously due to several limitations of this study. First, the results obtained may be due to chance because of the inadequate statistical power or bias inherent in case-control studies. Second, pathology reports were not available for all cases. However, we performed an analysis excluding those cases without pathology reports, and found that the positive association between rs1501299 in the *ADIPOQ* gene and pancreatic cancer remained unchanged. Third, we did not genotype SNPs that have been shown to be related to diabetes-related quantitative traits, including fasting plasma glucose, insulin, and homeostasis model assessment of β-cell function (HOMA-β). These biomarkers have been shown to be associated with pancreatic cancer risk in previous prospective studies[32,33]. Fourth, we did not examine serum levels of adiponectin in this study. Additional studies are necessary to clarify the effects of genetic polymorphisms on serum levels of adiponectin and evaluate their roles in the development of pancreatic cancer. Finally, we cannot exclude the possibility that the observed SNPs are in linkage disequilibrium with causal variants in the same gene or other genes. Further comprehensive analyses of SNPs in the two genes are required to identify the causal variants that confer susceptibility to diabetes or pancreatic cancer.

In summary, the results of our case-control study indicate that rs1501299 in the *ADIPOQ* gene may be associated with pancreatic cancer risk. These findings should be replicated in additional studies.

COMMENTS

Background

Given the well-recognized, positive association between type 2 diabetes and pancreatic cancer risk in epidemiological studies, it may be interesting to examine whether diabetes-related genetic variants may also be associated with pancreatic cancer risk.

Research frontiers

Although it is likely that a common genetic background predisposes individuals to developing both diabetes and pancreatic cancer, very few molecular epidemiologic studies have addressed this issue.

Innovations and breakthroughs

This case-control study indicates that rs1501299 in the *ADIPOQ* gene may be associated with pancreatic cancer risk in Japanese subjects.

Applications

Genetic variations in the adiponectin pathway may affect pancreatic cancer risk

through their effects on circulating adiponectin. Further comprehensive analyses of SNPs in this gene are required to identify the causal variants that confer susceptibility to diabetes or pancreatic cancer.

Terminology

Single-nucleotide polymorphisms (SNP) are the most common type of genetic variation among individuals. Some SNPs have been linked to increased susceptibility to disease.

Peer review

Very few molecular epidemiologic studies have addressed the issue about the common genetic background which predisposes individuals to developing both diabetes and pancreatic cancer. This a good case-control study, try to examine whether diabetes-related genetic variants are associated with pancreatic cancer risk in Japan. Seven diabetes-related genetic variants were therefore genotyped and it was found that rs1501299 in the *ADIPOQ* gene may be associated with pancreatic cancer risk, although the role of adiponectin variants has not been clarified yet.

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