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Genetic Variability in Energy Balance and Pancreatic Cancer Risk in a Population-Based Case-Control Study in Minnesota

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Abstract

Objectives—Accumulating evidence suggests that energy imbalance plays a role in pancreatic carcinogenesis. However, it remains unclear whether single nucleotide polymorphisms (SNPs) in genes regulating energy homeostasis influence pancreatic cancer risk. We investigated this question in a case-control study conducted from 1994 to 1998.

Methods—Cases (n=173) were ascertained from hospitals in the Twin Cities and Mayo Clinic, Minnesota. Controls (n=476) were identified from the general population and frequency matched to cases by age and sex. Seven SNPs were evaluated in relation to pancreatic cancer using unconditional logistic regression.

Results—After adjustment for confounders, the leucine/proline or proline/proline genotype of the neuropeptide Y (*NPY*) gene rs16139 was associated with a lower risk than the leucine/leucine genotype [odds ratio (OR) (95% confidence interval) (95% CI): 0.40 (0.15, 0.91)]. Conversely, an increased risk was observed for the glycine/arginine or arginine/arginine genotype of the adrenoceptor beta 2, surface (*ADRB2*) gene rs1042713 as compared with the glycine/glycine genotype [OR (95% CI): 1.52 (1.01, 2.31)].

Conclusions—This study first reveals that SNPs in genes modulating energy intake (*NPY*) and energy expenditure (*ADRB2*) altered pancreatic cancer risk. If confirmed by other studies, our findings may shed new light on the etiology and prevention of pancreatic cancer.

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Keywords

Pancreatic cancer; energy balance; obesity; polymorphisms; case-control study

INTRODUCTION

Pancreatic cancer is among the leading causes of cancer death in the United States and many other countries.[1,2] Worldwide, it is estimated that there are 227,000 deaths per year from this disease.[3] The etiology of pancreatic cancer is poorly understood, with cigarette smoking as one of the few established risk factors.[4] Primary prevention is particularly important for this disease because it is rapidly fatal and there is no population screening test available for early detection.[5] To prevent pancreatic cancer, it is important to elucidate its genetic and environmental causes.

Several lines of experimental and epidemiologic evidence suggest that energy imbalance is implicated in pancreatic carcinogenesis. Calorie restriction has inhibited the development of carcinogen-induced tumors in various animal models of cancer,[6] and in humans, a reduced risk of pancreatic cancer was observed in individuals of shorter than median stature who were exposed to energy restriction during adolescence in the period of the Economic Depression in the Netherlands.[7] Obesity develops as a consequence of long-term positive energy imbalance.[8] Obesity, physical inactivity, and type-2 diabetes have been associated with an increased risk of pancreatic cancer in most epidemiologic studies.[8–12] A potential mechanism underlying these associations is insulin resistance,[8,12] and the results of cohort studies showing that subjects with high serum levels of insulin and glucose (biomarkers of insulin resistance) are more likely to develop pancreatic cancer supports this view.[5,13]

A number of genes involved in the central and peripheral regulation of energy homeostasis have been identified.[14–16] Given the substantial experimental and epidemiologic evidence linking energy imbalance to the occurrence of pancreatic cancer, it is biologically plausible that polymorphisms in genes modulating energy intake and energy expenditure influence the risk of this malignancy. To date, few epidemiologic studies have investigated this hypothesis. Therefore, we sought to evaluate the associations between genetic variability in energy metabolism and the risk of pancreatic cancer in a population-based case-control study.

MATERIALS AND METHODS

Study Population

A case-control study was conducted from April 1994 to September 1998 in Minnesota and has been described in detail elsewhere.[17,18] Briefly, cases were persons who were diagnosed with pathologically-confirmed cancer of the exocrine pancreas (*International Classification of Disease for Oncology, third edition, code C25*). The cases were recruited from all hospitals in the seven-county metropolitan area of the Twin Cities (Minneapolis and St. Paul) and the Mayo Clinic and those ascertained from the Mayo Clinic were confined to residents in the Upper Midwest of the United States. Because a high proportion of patients with pancreatic cancer die soon after diagnosis, an ultra-rapid case-ascertainment system was adopted to quickly contact cases. As a result, the median number of days between diagnosis and first contact for the study was only 13 days. Patients with pancreatic cancer were eligible for the study if they were 20 years of age or older, English-speaking, and mentally competent to give informed consent. Of 460 eligible cases identified during the study period, 202 did not participate in the study due to occurrence of death before contact or interview (n = 85), refusal of cases (n = 79), refusal of physicians (n = 31), and inability

to contact cases (n = 7). After these exclusions, 258 cases participated in the study, producing a response rate of 56% among those identified.

The source population of the study was Upper Midwest of the United States and potential controls were randomly recruited from residents of the seven-county metropolitan area of the Twin Cities. Names were selected from the drivers' license and State identity card databases for subjects aged 20–64 years and from the Health Care Financing Administration (now called the Centers for Medicare and Medicaid Services) records for those aged 65 years or older. Controls were frequency matched to cases by age (within 5 years) and sex. Inclusion criteria for controls were the same as those for cases, with an exception of diagnosis of pancreatic cancer. A total of 1,141 eligible controls were identified, and 676 of them participated in the study, yielding a response rate of 59%. Of the 934 subjects (258 cases and 676 controls) who completed at least some portion of the study, genotyping data were not available for 259 subjects (69 cases and 190 controls) because they did not donate a blood sample or had an insufficient amount of remaining DNA samples for genotyping selected polymorphisms in the present study. Exclusion of subjects without the genotyping data resulted in 189 cases and 486 controls that had data required for the analysis of the present study. Of these subjects, only 16 cases and 10 controls were not of European descent and were excluded to avoid potential population stratification. Therefore, a total of 173 cases and 476 controls were available for the current analysis. Written, informed consent was obtained from all study participants prior to their interview. The protocol for this case-control study was approved by the Institutional Review Boards of the University of Minnesota and the Mayo Clinic.

Data Collection—Cases and controls were interviewed in person to collect information on demographics, education level attained, physical activity, medical history, and cigarette smoking. Subjects were asked to report a history of type 2 diabetes mellitus. Since incident diabetes that occurs less than 2 years prior to pancreatic cancer can be a symptom of pancreatic cancer,[19,20] subjects diagnosed with diabetes less than 2 years before their cancer diagnosis (cases) or selection dates (controls) were treated as not having diabetes. During the interview, usual diet of cases and controls was assessed by a slightly modified version of the Willett food frequency questionnaire (FFQ), a validated dietary assessment instrument widely used in nutritional epidemiologic studies.[21] Calculating intakes of energy and nutrients was based on the responses of subjects on all food items listed in the modified Willet FFQ and a nutrient database developed for the Minnesota Colon Cancer Prevention Research Unit studies. As a section of the FFQ used, habitual consumption of alcoholic beverages (including wine, beer, and liquor) was estimated in the same way as intake of energy and nutrients.

Genotyping

DNA samples were extracted from peripheral blood lymphocytes with a commercial kit (Qiagen Inc., Valencia, CA). The single nucleotide polymorphisms (SNPs) considered in this study were leptin (*LEP*) (rs7799039), leptin receptor (*LEPR*) (rs1137101), ghrelin/obestatin prepropeptide (*GHRL*) (rs696217), neuropeptide Y (*NPY*) (rs16139), adrenoceptor beta 2, surface (*ADRB2*) (rs1042713), adrenoceptor beta-3 (*ADRB3*) (rs4994), and uncoupling protein 3 (mitochondrial, proton carrier) (*UCP3*) (rs1800849). These SNPs were selected because 1) their genes regulate energy intake (*LEP*, *LEPR*, *GHRL*, and *NPY)* or energy expenditure (*ADRB2*, *ADRB3*, and *UCP3)*,[14,15,22] 2) they have established or potential functional impact;[14,23–30] the five of the seven selected SNPs are missense mutations (rs7799039 and rs1800849 are not missense), and 3) they are common (minor allele frequency >5%) among European Americans (the NCBI SNP database: http://www.ncbi.nlm.nih.gov). SNP genotyping was conducted with TaqMan SNP Genotyping

Assays (Life Technology, Grand Island, NY) in a laboratory (Fred Kadlubar, PhD) of the Division of Medical Genetics, University of Arkansas for Medical Sciences. To minimize genotyping error, several quality control measures were taken that include the blinding of genotyping personnel to the case-control status of DNA samples and a random replication of 10% of the tested samples. The concordance was found to be 100% for the replicated samples.

Statistical Analysis

All measured SNPs were tested for their deviation from the Hardy-Weinberg equilibrium among controls. The demographic, lifestyle, and other characteristics of cases and controls were compared using the t-test for continuous variables and the chi-square test for categorical variables. The associations between genotyped SNPs and pancreatic cancer risk were evaluated by unconditional logistic regression analysis. With subjects who were homozygous for wild-type alleles of a SNP as the referent category, odds ratios (OR) and 95% confidence interval (95% CI) were estimated for those who were heterozygous or homozygous for variant alleles. Considering the relatively small number of cases (n=173), individuals who carried one or two copies of variant alleles were combined into one category to improve the precision of risk estimates. To investigate the independent effect of measured SNPs on pancreatic cancer risk, age, sex, education (three levels), cigarette smoking (never, former, and current), and alcohol intake (servings/week) were added as covariates to logistic regression models.

Haplotype analysis was not performed because none of the seven SNPs examined were correlated with each other (all $r^2 \leq 0.002$) and only two SNPs (rs7799039 and rs16139) are on the same chromosome (#7). The potential interactions of these SNPs with lifestyle factors that could influence energy balance and insulin resistance (i.e. physical activity and dietary intake of energy, fat, and fiber)[31] were evaluated in relation to the risk of pancreatic cancer. The statistical significance of interaction terms was assessed with the likelihood ratio test. All statistical analyses were conducted with SAS (version 9.3; SAS Institute, Inc., Cary, NC). Given that only seven SNPs were evaluated in our study and that all of these genetic variants have established or potential functionality, the significance level (type I error) for the associations between genotyped SNPs and pancreatic cancer risk was not corrected for multiple comparisons. A two-sided p-value of <0.05 was considered statistically significant.

RESULTS

Demographic, lifestyle, and other characteristics of cases and controls were compared (Table 1). The mean age of cases and controls was 66.2 years and 65.6 years, respectively. Males constituted 59.9% of cases and 56.9% of controls. Cases were statistically significantly less educated and physically inactive than controls, whereas history of type 2 diabetes was more common in cases than in controls.

All SNPs examined in this study were in Hardy-Weinberg equilibrium (all p>0.28), which offers evidence supporting the accuracy and validity of the genotyping procedure. The results for pancreatic cancer risk in relation to measured SNPs were presented in Table 2. After adjustment for age, sex, education, smoking status, and alcohol intake, individuals who were heterozygous [leucine (Leu)/proline (Pro)] or homozygous (Pro/Pro) for the variant allele of *NPY* rs16139 experienced a 60% lower risk of pancreatic cancer than those who were homozygous for the wild-type allele [OR (95% CI): 0.40 (0.15, 0.91)]. Conversely, a significantly increased risk was observed for subjects who harbored one or two copies of the variant allele of ADRB2 rs1042713 [OR (95% CI): 1.52 (1.01, 2.31) for glycine (Gly)/Arginine (Arg) and Arg/Arg vs. Gly/Gly]. Other SNPs analyzed in this study were not significantly associated with the risk of pancreatic cancer. Adjustment for age only

virtually did not alter the risk estimates for all selected SNPs that were obtained from models without adjustment for any covariates. In addition, no statistically significant interactions were observed on the disease risk for any combinations of the genotyped SNPs and lifestyle factors considered.

DISCUSSION

In this population-based case-control study, we found that genetic variability in the regulation of energy balance was associated with a statistically significant change in pancreatic cancer risk. To our knowledge, the significant associations between polymorphisms *NPY* rs16139 and *ADRB2* rs1042713 and the risk of pancreatic cancer have not been reported in previous epidemiologic studies.

Recent advances in human genomics have identified genes implicated in the central and peripheral regulation of energy homeostasis.[14,15,22] The genes that control food intake include peripheral signal peptides (e.g., *LEP* and *GHRL*), central neuropeptides (e.g., *NPY*), and their corresponding receptors.[14] Some of the genes that modulate energy expenditure are *ADRB2*, *ADRB3*, and *UCP3*.[14] It is reasonable to hypothesize that functional polymorphisms in these genes governing energy balance are associated with pancreatic cancer risk through their effects on obesity and resultant insulin resistance. However, this hypothesis has not been investigated in previous epidemiologic studies.

NPY is an appetite stimulator secreted in the hypothalamus and is regulated by the feedback of ghrelin and leptin. While ghrelin stimulates appetite during fasting, leptin is released after eating.[14] A nonsynonymous SNP (rs16139) in the *NPY* gene results in an amino acid change from Leu to Pro at codon 7 (Leu7Pro).[29] A study of 14 healthy Caucasian men showed that carriers of the Pro7-allele exhibited elevated plasma levels of NPY compared with noncarriers.[32] In a Dutch study, male carriers of the Pro7-allele had higher leptin levels and BMI values than non-carriers of this allele[25]. The association between this genetic variant and obesity is inconsistent across epidemiologic studies, although most studies reported that individuals who harbored the Pro7-allele had a greater body mass index (BMI) than those who did not.[25,26,29,33] In a case-control study, the variant allele (Pro7-allele) conferred an increased risk of follicular lymphoma.[29] The present study showed that subjects who were heterozygous or homozygous for the Pro7-allele had a 60% lower risk of pancreatic cancer than those who were homozygous for the Leu7-allele. This finding is not in line with the functional impact of the *NPY* rs16139 polymorphism if its effect is only to increase BMI. This inconsistency may be explained by several factors. Some studies revealed that increased BMI associated with this polymorphism was not observed among obese or insulin-resistant individuals,[33,34] subgroups with higher risk for pancreatic cancer.[8,12] In addition, NPY was also found to be pleiotropic, i.e. it may affect the development of pancreatic cancer through mechanisms other than increased BMI. NPY has been found to regulate energy expenditure, independent of food intake,[35] and to modulate immune functions through its expression in lymphoid tissue and the expression of its receptors in immune cells.[36]

ADRB2 is a member of the G protein-coupled adrenergic receptor superfamily and participates in the peripheral regulation of energy expenditure.[14] Expressed in abdominal subcutaneous adipose tissue, ADRB2 mobilizes lipids within human fat cells by stimulating lipolysis.[30,37] A common polymorphism in ADRB2 (rs1042713) leads to an amino acid substitution at codon 16 (Gly16Arg).[14] Experimental studies have demonstrated that this sequence variant altered the function of the beta-2 adrenoceptor.[38] It has been reported that subjects carrying the Gly16 allele exhibited a fivefold increased agonist sensitivity in absence of any change in the expression of this receptor.[38] Epidemiologic studies have

observed the associations of this polymorphism with obesity, diabetes, and plasma lipid levels, but results are not entirely consistent.[16] In one study, the Arg16 allele was associated with an increased BMI after adjustment for demographic variables, blood lipids, and diabetes.[39] In another study, individuals with two copies of the Arg16 allele had an 87% higher risk of diabetes than those with zero or one copy of this allele.[37] In the present study, we found that heterozygosity or homozygosity of the Arg16 allele was associated with a 52% elevated risk of pancreatic cancer, as compared with homozygosity of the Gly16 allele. This association was statistically significant and consistent with the findings of previous epidemiologic studies that identified the Arg16 allele as a risk factor for obesity and diabetes.[37,39]

We also examined the effect of polymorphisms in other genes involved in the regulation of energy intake [*LEP* (rs7799039), *LEPR* (rs1137101), and *GHRL* (rs696217)] and energy expenditure [*ADRB3* (rs4994) and *UCP3* (rs1800849)] on pancreatic cancer risk (Table 2). None of these polymorphisms was significantly associated with the risk of pancreatic cancer. Accumulating evidence suggests that these genetic variants are functional because each of them is associated with either altered levels of protein (e.g. *LEP*)[40] or risk of weight gain or obesity.[41–44] Although none of these SNPs has been evaluated in relation to pancreatic cancer risk in previous epidemiologic studies, a *LEPR* polymorphism (rs1137101) significantly modulated the risk of breast cancer.[45] A possible explanation for our observed null associations with the aforementioned SNPs is that the effects of these SNPs might be modest and could not be detected due to the relatively small sample size of the present study.

There are some limitations inherent in the present study. Response rates for both cases and controls were less than 60%. Selection bias might have occurred due to the low response rate. It is unlikely that control respondents were significantly different from non-respondents with regard to the allele frequencies of candidate genes. However, if survival in cases is related to any of the SNPs considered or their associated phenotypes, our findings could be altered. Genotyping error should be considered in any genetic association studies. As stated above, all seven SNPs examined were in Hardy-Weinberg Equilibrium, and 10% of replicated DNA samples were 100% concordant, which suggests that genotyping error, if any, should be small in our study. The two polymorphisms significantly associated with pancreatic cancer risk in this study may simply be markers that are in linkage disequilibrium with unmeasured polymorphisms that are causally associated with this disease. BMI was not collected in this study due to an oversight, which precludes us from testing its interactions with the SNPs examined on pancreatic cancer risk. The lack of BMI data is not viewed as a limitation for analysis of the genetic variants and pancreatic cancer because BMI, like energy intake, physical activity, and diabetes, may be on the causal pathway between the selected SNPs and pancreatic cancer and therefore should not be treated as a potential confounder in constructed logistic regression models.

In summary, the present study revealed that two polymorphisms in the genes regulating energy homoeostasis are associated with an altered risk of pancreatic cancer. If confirmed by other epidemiologic studies, these findings lend further support to the role of obesity and diabetes in the etiology of this malignancy and underscore the importance of preventing these conditions as strategies for its primary prevention.

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Table 1

Characteristics of cases and controls in a population-based case-control study of pancreatic cancer in Minnesota, 1994–1998*

Characteristic	Cases (n=173)	Controls (n=476)	*P* value
Age (years)†	66.2 (11.4)	65.6 (12.4)	0.54
Sex			
Male	103 (59.9%)	271 (56.9%)	
Female	69 (40.1%)	205 (43.1%)	0.50
Education			
Some high school or less	25 (14.5%)	53 (11.1%)	
High school graduate	66 (38.4%)	121 (25.4%)	
Some college or more	81 (47.1%)	302 (63.5%)	0.0008
Physical activity (hour/week) †	43.6 (26.6)	50.2 (25.6)	0.009
Cigarette smoking			
Never smoker	69 (41.8%)	219 (46.0%)	
Former smoker	70 (42.4%)	203 (42.7%)	
Current smoker	26 (15.8%)	54 (11.3%)	0.30
Alcohol intake (serving/week)†	3.4 (7.0)	4.7 (8.5)	0.08
Energy intake (kcal/day) †	2,106 (967)	2,102 (834)	0.96
Diabetes‡			
Yes	14 (8.1%)	5 (1.1%)	
No	159 (91.9%)	471 (98.9%)	<0.0001

*Data for some variables were missing for cases and/or controls.

†Values given are mean (standard deviation).

‡Defined as diabetes diagnosed ≥2 years prior to pancreatic cancer diagnosis

Table 2

Risk of pancreatic cancer in relation to SNPs in genes involved in energy balance in a population-based case-control study of pancreatic cancer in Minnesota, 1994–1998

	Cases (n=173)		Controls (n=476)		
Gene	**Number**	**%**	**Number**	**%**	**OR (95% CI)***
Regulating Energy Intake					
LEP (−2548G>A) (rs7799039)					
GG	51	29.5	158	33.2	1.00†
AG or AA	122	70.5	318	66.8	1.13 (0.74, 1.76)
LEPR (Gln223Arg) (rs1137101)					
Gln/Gln	60	34.7	144	30.3	1.00†
Gln/Arg or Arg/Arg	113	65.3	332	69.8	0.85 (0.56, 1.31)
GHRL (Leu72Met) (rs696217)					
Leu/Leu	138	79.8	397	83.4	1.00†
Leu/Met or Met/Met	35	20.2	79	16.6	1.17 (0.70, 1.93)
NPY (Leu7Pro) (rs16139)					
Leu/Leu	167	96.5	431	90.6	1.00†
Leu/Pro or Pro/Pro	6	3.5	45	9.4	**0.40 (0.15, 0.91)**
Regulating Energy Expenditure					
ADRB2 (Gly16Arg) (rs1042713)					
Gly/Gly	65	37.6	209	43.9	1.00†
Gly/Arg or Arg/Arg	108	62.4	267	56.1	**1.52 (1.01, 2.31)**
ADRB3 (Trp64Arg) (rs4994)					
Trp/Trp	29	16.8	76	16.0	1.00†
Trp/Arg or Arg/Arg	144	83.2	400	84.0	1.24 (0.72, 2.24)
UCP3 (−55C>T) (rs1800849)					
CC	98	56.7	273	57.4	1.00†
CT or TT	75	43.3	203	42.7	0.99 (0.66, 1.48)

Abbreviations: Gln, Glutamine; Arg, Arginine; Leu, Leucine; Met, Methionine; Pro, Proline; Gly, Glycine; Trp, Threonine; *LEP*, leptin; *LEPR*, leptin receptor; *GHRL*, ghrelin/obestatin prepropeptide; *NPY*, neuropeptide Y; *ADRB2*, adrenoceptor beta 2, surface; *ADRB3*, adrenoceptor beta-3; *UCP3*, uncoupling protein 3 (mitochondrial, proton carrier).

* Adjusted for age, sex, education, smoking status, and alcohol intake.

† Reference.