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Genetic variants of peroxisome proliferator-activating receptor δ are associated with gastric cancer

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Abstract

Background—Peroxisome proliferator-activating receptors (PPAR) are implicated in pathogenesis of insulin resistance and cancers of the digestive system.

Aim—We investigated the associations of single nucleotide polymorphisms (SNPs) of peroxisome proliferator-activating receptors δ and γ with gastric cancer and explored interactions with risk factors of gastric cancer.

Methods—We conducted our analysis in a case-control study of 196 gastric cancer patients and 397 controls residing in Taixing region of Jiangsu, China. Six SNPs in the PPARδ (rs2076167, rs3734254) and PPARγ genes (rs10865710, rs1801282, rs3856806, rs13306747) were genotyped. We employed logistic regression to evaluate the association between each genotype and gastric cancer and tested for gene-environment interaction with *Helicobacter pylori* infection, smoking status, and meat and salt intake.

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Results—We found that the G/G variant rs2076167, in tight linkage disequilibrium with rs3734254 (R^2=0.97), was associated with increased risk of gastric cancer in a recessive model (OR = 2.20, 95%1.12, 4.32). The association between G/G variant of rs2016167 and gastric cancer was particularly strong among those with higher salt intake (OR = 5.11, 95% 1.11, 23.5), but did not vary by *Helicobacter pylori* infection, or smoking status.

Conclusion—We found that genetic variants of PPARδ were associated with gastric cancer. If the association is confirmed in larger studies, it may implicate a role for PPARδ activators, such as insulin-sensitizing agents, in prevention of gastric cancer.

Keywords

peroxisome proliferator-activating receptors; gastric cancer; gene-environment interaction; salt

Introduction

Gastric cancer is the sixth most commonly occurring cancers in the world, newly afflicting an estimated 990,000 and killing 737,000 patients per year [1]. It is also the most common cancer in East Asian populations [2]. Family history is considered a potential risk factor for gastric cancer that might be partially influenced by clustering of *H. pylori* infection, diet, and other shared environmental exposures within the family [3]. On the other hand, it may also suggest that genetics may play an important role in gastric cancer burden as shared genetic mutations have been found in familial gastric cancer clusters [4]. Among few genes that have been found to be associated with gastric cancer, variations in genes that encode for peroxisome proliferator-activating receptors (PPAR) may be associated with gastric cancer, given the regulatory role of PPARs in cell proliferation and cell differentiation, which promotes tumorigenesis and cancer progression [5, 6] as well as the abundant expression PPAR in the digestive tract [7]. Previous studies on PPARs and gastric disease shows that the Pro12Ala variant of PPARγ (rs1801282) is associated with gastric cancer, peptic ulcer disease, and impaired fasting glucose in Japanese individuals[8, 9]. These studies also showed potential for interaction with *Helicobacter pylori* (*H. pylori*) infection, as the effect of PPARγ was elevated in *H. pylori* infected individuals. Given that PPARs may also interact with other 'environmental' factors, there is a need for further studies on gene-environmental interaction between genetic variants and smoking, dietary factors, such as salt and meat, that have also been implicated in gastric cancer pathogenesis[9, 10].

Methods

Study population

The study population was recruited from Taixing county, located in the Jiangsu province of southeast China. We recruited cases with cancers in three different sites, esophagus, stomach and liver, and one common control group for all types of cases. Patients were eligible for the study if they were reported to the Taixing Tumor Registry at the Taixing Center for Disease Control as having newly diagnosed stomach cancer based on ICD-9 codes between June, 1st 2000 to December 30th, 2000, were at least 20 years of age, lived in Taixing for 10 or more years. Of 316 stomach cancer patients diagnosed in Taixing, 206 cases were eligible and willing to participate in the study. Control population was selected from healthy individuals randomly from the general population in Taixing who were also at least 20 years of age and lived in Taixing for 10 or more years. Age, sex, residential area (village or city block) were frequency matched between the esophageal, stomach and liver cancer cases and controls in a 3:2 ratio. There were 464 controls invited to participate, of whom 415 consented. DNA from blood samples were available from 196 stomach cancer cases and 397 controls.

Data

The study participants were interviewed in person at their home, hospital or the doctor's office. Cases were interviewed within 3–6 months of the diagnosis. The questionnaire solicited information on the demographic data, socioeconomic status, family history of cancer, smoking history, alcohol consumption, and diet. Other questions relevant for development of stomach cancer, such as use of refrigerator, and relative hotness (temperature) of food were also asked. A food-frequency questionnaire (FFQ) was used to collect dietary history on general patterns a year before the interview for controls, and a year before diagnosis for cases. The development and validation of a similar FFQ used for Han Chinese in Shanghai have been reported [11, 12]. In total, 97 specific foods according to the customs of local residents and 33 specific Chinese dietary items were selected for investigation. Each participant was asked to report frequency of intake per day, week, month, or year, and the usual serving size of each food item during the past year. For the purpose of assessing the relative consumption of meat, we computed the amount of pork, beef/mutton, bird meat and fish consumed in units of kg/month and summed it as a composite measure. For salt consumption, the participants were asked how much salt was consumed per household every month. The individual salt intake was determined by dividing the household salt consumption by the number of people in the household. Participants were categorized into 1^{st} to 4^{th} quartile of meat or salt consumption based on distributions of intake in the controls.

Laboratory methods

Six SNPs in the PPARδ (rs2076167, rs3734254) and PPARγ genes (rs10865710, rs1801282, rs3856806, rs13306747) were selected for genotyping. Genotypes of the SNPs were determined by Applied Biosystems TaqMan assay (ABI, Foster City, CA). PCR reactions were run in a total volume of 5 ul with fluorescently labeled sequence-specific probes and primers using the following protocol: denaturation at 92 °C for 10 min, 60 cycles at 92 °C for 15 sec extension at 62 °C for 80s. The genotypes were detected using the ABI 7900HT Sequence Detection System with SDS 2.3 software. Hardy-Weinberg equilibrium (HWE) of the genotypes were tested using Fisher's exact test and SNPs were considered to be in violation of HWE at p-value of <0.05. Linkage disequilibrium was assessed by computing the Pearson correlation coefficient of the minor allele frequencies for each SNP pairs. Call rates were 90% or higher for all genotypes.

Infection with *H. pylori* was determined by testing for CagA+ *H. pylori* antibodies in the blood using an indirect enzyme immunoassay technique with kits from the Reagent Company of the Shanghai Biotechnology Industry Park (Pudong, Shanghai, China).

Statistical Analysis

Associations between genotypes of selected SNPs and gastric cancer were examined using 1) the monotonic-response model by treating the frequency of minor allele as an ordinal variable (0, 1, or 2), 2) the dominant model and 3) the recessive model. Associations between the covariates and gastric cancer were examined using logistic regression. Confounder-adjusted association were examined by conducting multivariable regression including age, sex, BMI (<24 kg/m2, ≥24 kg/m2), education level (less than primary school, primary school, middle school or higher), income 10 years before (<=100 RMB/month, >100 RMB/month), family history of stomach cancer, smoking (never, <20, ≥20 pack-years), *H. pylori* infection, refrigerator use, relative temperature of tea, soup, porridge consumed (very hot vs. hot or moderate), meat and salt consumption (quartile distribution). Genotype(s) associated with gastric cancer were further analyzed for potential effect modification by risk factors of gastric cancer. Significance of effect modification was tested by including two-way interaction terms in the multivariable model and ORs for the

relationship between SNPs and gastric cancer were presented for each stratum-specific analysis. The significance of the associations were evaluated at $p<0.05$ for the association between the variables and gastric cancer. All statistical analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC).

Results

The demographic, social characteristics of the study population are presented Table 1. The mean age of the study population was 59 years, and 68% were male. In bivariate analyses, cases were less likely to have completed middle school, to make >100 RMB/month, and more likely to have smoked more than 20 pack-years, have a family history of stomach cancer, eat very hot foods. Cases were also less likely to use refrigerator and ate less meat overall compared to the controls (Table 1). In multivariable model analyses we found that smoking >=20 pack years of more was associated with gastric cancer compared to non smoking (adjusted OR = 1.98, 95% CI 1.03, 3.79). In the same model, family history of stomach cancer (adjusted OR = 6.30, 95%CI 2.92, 13.6) and consumption of very hot food (OR = 2.25, 95%CI 1.13, 4.45) were strongly associated with gastric cancer. High levels of meat consumption also remained a protective factor for gastric cancer (OR = 0.23, 95% CI 0.11, 0.48) in the multivariable model (Table 1).

Two SNPs (rs10865710 and rs1801282) in PPARγ did not meet the Hardy-Weinberg equilibrium criteria and were thus excluded. SNP rs3734254 of the PPARδ gene was in tight linkage disequilibrium with rs2076167 in the same gene ($R^2 = 0.97$). We conducted analyses with rs2076167, which had a higher call rate (92.2% vs. 90.2%). In monotonic response model, G allele of the rs2076167 was associated with gastric cancer, while there was no association between PPARγ SNPs and gastric cancer. The recessive model showed that the G/G genotype was associated with gastric cancer (OR=1.98, 95%CI (1.03, 3.80)), while no obvious association was observed on the G/A genotype in the co-dominant model (OR = 1.25, 95%CI (0.87, 1.80)). (Table 2)

In multivariable model, education level and higher level of meat consumption were inversely associated with gastric cancer, while smoking, family history of stomach cancer, and consumption of very hot food were positively associated with gastric cancer. (Table 1)

When the association between rs2076167 genotype and gastric cancer were assessed by strata of risk factors considered in the multivariable analysis, we found the G/G genotype was not statistically associated with gastric cancer in substrata of BMI, smoking, *H. pylori*, or meat consumption. On the other hand, the association between rs2076167 and gastric cancer was strengthened (OR = 5.11, 95%CI (1.11, 23.5) for those with high salt consumption (>0.50kg/month). The test for significance of interaction was positive only for salt consumption. The stratum-specific analyses were not presented for family history of cancer and consumption of very hot food, because of the lack of G/G carriers in at least one of the strata. (Table 3)

Discussion

Our study showed that the G/G variant of rs2016167 in the PPARδ gene was associated with gastric cancer. Previous studies on polymorphisms in PPAR genes and gastric cancer had found that PPARγ Pro12Ala was associated with gastric cancer and peptic ulcer disease [8, 9]. This PPARγ polymorphism (rs1802282) was not in HWE in our study and therefore we could not validate the finding from the previous study.

While little is known about the role of PPARδ in the stomach, it is reported that PPARδ is highly expressed in organs in the digestive tract [7] and that PPARδ is involved in the

regulation of cell proliferation/differentiation and modulation of inflammatory disease in the digestive tract[6]. Furthermore, pharmacologic agents that activate PPARδ, such as thiazolidinediones, have been inversely associated with epithelial cancers, such as lung, colorectal and breast cancer [13], adding credence to a potentially true causal relationship between PPARδ and the development of gastric cancer. Literature points to the involvement of PPARδ with the NF-kB, interleukin-1b, cyclooxygenase-2 and the Wnt-beta-catenin/TCF-4 pathways that have all been implicated in gastric cancer pathogenesis[14]. However, animal model studies of tumorigenesis have led to conflicting findings regarding the role of PPARδ in the digestive tract[14]. While some animal model studies demonstrate an anti-carcinogenic role of PPARδ expression in liver, small intestine and colon[15–17], other studies showed neutral or a pro-carcinogenic tendency for PPARδ expression and ligand activation[18, 19]. Further studies on the functional characterization of PPARδ and effects of different PPARδ agonists will clarify the role of PPARδ in tumorigenesis and how drugs could target PPARδ for reduction in risk of gastric cancer.

The association between G/G variant PPARδ SNP rs2076167 was particularly strong in those with higher salt consumption, but our finding was limited by small sample size with less than 10 individuals in controls consuming a higher level of salt. Although higher doses of salt consumption was not obviously associated gastric cancer in our study, high consumption of salt and salty foods has been reported to be a risk factor for gastric cancer in multiple observational studies, particularly in Asia[13]. Salt and salted foods are hypothesized to increase the risk of gastric cancer by enhancing *H. pylori* colonization and by inducing endogenous mutations that collectively cause genomic stability, one of the hallmarks of cancer[20]. Our study shows the potential for gene-environment interaction between PPAR genes and salt intake on gastric cancer. The G/G variant of the PPARδ gene may function to enhance the mutagenic effect of salt in promoting cancer. The biological mechanism of this interaction may also involve the dynamic relationship of PPAR and Na+/H+ transporters, which regulates the pH of the cellular environment. Normal activation of PPAR represses Na+/H+ transporter expression[21]. A defective PPAR may lead to over-expression of Na+/H+ transporter, which will transport Na+ into the cells down the gradient when salt concentration is high in the extracellular space, while transporting H+ out of the cells and therefore create an alkaline (higher pH) environment fit for cell proliferation and survival[22].

Our study was limited by the sample size, which may have led to suboptimal power to detect true associations in stratum-specific analyses. Also, the study was conducted in a retrospective manner, in which recall bias may have affected response to dietary measures. Also, the study was conducted in a retrospective manner, in which recall bias may have affected response to dietary measures. For example gastric cancer patients may have reported their diet prior to diagnosis more accurately, compared to controls, in consideration of their cancer diagnosis. Furthermore, gastric cancer cases were not anatomically or histologically classified (i.e. cardia vs. non-cardia; diffuse vs. intestinal), the distinction of which has been important for the pathogenic mechanisms of risk factors such as *H. pylori*[23]. In addition, we lacked data on CagA negative *H. pylori* infection, which may also increase the risk of gastric cancer. While it is unlikely that the finding of the PPARδ SNP and gastric cancer would have been confounded by this unmeasured factor, it may have limited our ability to detect a possible interaction between PPARδ SNP and *H. pylori* infection. Furthermore, it has been reported that gastric cancer could potentially lead to loss of CagA positive *H. pylori* infection [24]. Thus the post-diagnosis assessment of H. pylori might have led to misclassification of previous CagA positive H. pylori infection, thus preventing us from establishing CagA positive H. pylori infection as a risk factor for gastric cancer in our study.

Our study was the first to document the relationship between PPARδ and gastric cancer. This relationship should be validated in larger prospective studies. If confirmed, our findings suggest that PPARδ agonists, such as thiazolidinediones, may have a protective effect against gastric cancer.

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Table 1

Characteristics of stomach cancer cases and controls in Taixing, China

Variable	Category	Gastric Cancer (n, %)	Control (n, %)	OR (95% CI)	Adjusted OR* (95% CI)
Total N		206 (100%)	415 (100%)		
Age (mean in years, SD)		61 (9.8)	58 (12)	1.03 (1.02, 1.05)	0.99 (0.97, 1.02)
Male		138 (67%)	287 (69%)	0.86 (0.59, 1.25)	1.12 (0.59, 2.14)
BMI (≥24.0 kg/m2)		31 (15%)	91 (22%)	0.63 (0.39, 1.00)	0.80 (0.45, 1.44)
Education					
	Illiteracy	66 (32%)	73 (18%)	Ref	Ref
	primary school	107 (52%)	142 (34%)	0.91 (0.59, 1.41)	0.96 (0.54, 1.69)
	middle school or higher	33 (16%)	200 (48%)	0.17 (0.10, 0.29)	0.15 (0.07, 0.33)
Monthly Income per capita 10 years ago (yuan)					
	≤100	136 (66%)	229 (55%)	Ref	Ref
	> 100	70 (34%)	186 (45%)	0.67 (0.47, 0.96)	0.84 (0.53, 1.31)
Smoking					
	Never smoker	92 (46%)	217 (52%)	Ref	Ref
	< 20 pack years	42 (21%)	85 (21%)	1.18 (0.75, 1.87)	1.78 (0.91, 3.49)
	≥20 pack years	67 (33%)	112 (27%)	1.54 (1.02, 2.30)	1.98 (1.03, 3.79)
Helicobacter pylori infection		71 (35%)	114 (31%)	1.16 (0.79, 1.70)	1.40 (0.89, 2.19)
Family history of stomach cancer		37 (18%)	22 (5.3%)	3.57 (1.98, 6.43)	6.30 (2.92, 13.6)
Very hot food (temperature)		30 (15%)	30 (7.3%)	2.24 (1.29, 3.90)	2.25 (1.13, 4.45)
Refrigerator use		21 (11%)	86 (22%)	0.45 (0.27, 0.76)	0.69 (0.37, 1.30)
Meat (composite score)					
	1st quartile (<1 kg/month)	83 (40%)	104 (26%)	Ref	Ref
	2nd quartile (1–2.625 kg/month)	60 (29%)	101 (25%)	0.65 (0.42, 1.03)	0.85 (0.49, 1.48)
	3rd quartile (2.626 – 5.433 kg/month)	43 (21%)	103 (25%)	0.47 (0.29, 0.76)	0.83 (0.46, 1.51)
	4th quartile (>5.433 kg/month)	20 (9.7%)	102 (25%)	0.21 (0.12, 0.38)	0.23 (0.11, 0.48)
Salt					
	1st quartile (≤188 g/month)	47 (23%)	110 (28%)	Ref	Ref
	2nd quartile (188–250 g/month)	67 (33%)	102 (26%)	1.53 (0.95, 2.46)	1.42 (0.81, 2.52)
	3rd quartile (251–375 g/month)	47 (23%)	108 (27%)	0.97 (0.59, 1.60)	0.89 (0.48, 1.66)

Variable	Category	Gastric Cancer (n, %)	Control (n, %)	OR (95% CI)	Adjusted OR* (95% CI)
	4th quartile (>375g/month)	41 (20%)	77 (19%)	1.17 (0.69, 1.99)	1.08 (0.57, 2.08)

*Adjusted for all factors listed in the table

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Table 2

Association between PPARδ and PPARγ SNPs and gastric cancer - unadjusted model

SNP	Comparison	Gastric Cancer (n, %)	Control (n, %)	Monotonic-response model OR (95% CI)	P for trend
PPARδ rs2076167					0.03
	A/A	86 (45%)	199 (52%)	Ref	
	A/G vs. A/A	88 (46%)	163 (43%)	1.25 (0.87, 1.80)	0.25
	G/G vs. A/A	19 (9.8%)	20 (5.2%)	2.20 (1.12, 4.32)	0.01
	A/G+G/G vs. A/A			1.35 (0.96, 1.92)	0.09
	G/G vs A/G+A/A			1.98 (1.03, 3.80)	0.04
PPARγ rs3856806					0.51
	C/C	104 (54%)	220 (57%)	Ref	
	C/T vs. C/C	75 (39%)	141 (37%)	1.13 (0.78, 1.62)	0.53
	T/T vs. C/C	12 (6.3%)	22 (5.7%)	1.15 (0.55, 2.42)	0.71
	C/T+T/T vs. C/C			1.13 (0.80, 1.60)	0.50
	T/T vs. C/T+C/C			1.10 (0.53, 2.27)	0.80
PPARγ rs13306747					0.76
	C/C	174 (92%)	347 (92%)	Ref	
	C/G vs. C/C	15 (7.9%)	29 (7.7%)	1.03 (0.54, 1.98)	0.98
	G/G vs. C/C	0 (0%)	2 (0.5%)	N/A	
	C/G+G/G vs. C/C			0.97 (0.51, 1.84)	0.91
	G/G vs. C/G+C/C			N/A	

Table 3

Association between PPARδ rs2076167 (G/G vs. A/A or A/G) and stomach cancer by potential effect modifiers

Variable	Cases	Controls	Crude OR (95% CI)	Adjusted OR (95%CI)	P for interaction
	G/G vs A/G + A/A	G/G vs A/G + A/A			
Lower BMI	15/139	12/248	2.17 (1.03, 4.57)	1.63 (0.65, 4.13)	0.94
Higher BMI	2/13	5/67	1.58 (0.37, 6.79)	1.45 (0.18, 11.8)	
Never smoker	6/77	9/161	1.14 (0.42, 3.16)	1.36 (0.33, 5.64)	0.49
Ever smoker	12/86	8/154	2.97 (1.17, 7.51)	1.97 (0.65, 5.96)	
Helicobacter pylori uninfected	10/107	9/217	2.36 (0.95, 5.86)	1.83 (0.60, 5.58)	0.71
Helicobacter pylori infected	8/56	8/98	1.75 (0.63, 4.93)	1.51 (0.39, 5.88)	
Lower meat	16/111	9/154	2.11 (0.97, 4.58)	2.04 (0.77, 5.40)	0.48
Higher meat	2/52	8/161	0.83 (0.17, 4.02)	1.14 (0.16, 8.15)	
Lower salt	8/86	11/153	0.89 (0.35, 2.27)	0.73 (0.24, 2.28)	0.02
Higher salt	10/76	6/161	4.84 (1.74, 13.4)	5.11 (1.11, 23.5)	

Adjusted for all variables listed in Table 1