Published in final edited form as:
Clin Cancer Res. 2009 January 15; 15(2): 740–746. doi:10.1158/1078-0432.CCR-08-1607.

DNA Repair Gene Polymorphisms and Risk of Pancreatic Cancer

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Abstract

Purpose—The current research was undertaken to examine the association between genetic variations in DNA repair and pancreatic cancer risk.

Experimental Design—We analyzed nine single nucleotide polymorphisms (SNPs) of seven DNA repair genes (*LIG3*, *LIG4*, *OGG1*, *ATM*, *POLB*, *RAD54L*, and *RECQL*) in 734 patients with pancreatic adenocarcinoma and 780 healthy controls using the Taqman method. Information on cigarette smoking, alcohol consumption, medical history, and other risk factors was collected by personal interview.

Results—The homozygous mutant genotype of *LIG3* G-39A (odds ratio [OR], 0.23; 95% confidence interval [CI] = 0.06-0.82; $P = 0.027$) and *ATM* D1853N (OR, 2.55; 95% CI = 1.08-6.00; $P = 0.032$) was significantly associated with altered risk for pancreatic cancer. A statistically significant interaction of *ATM* D1853N and *LIG4* C54T genotype with diabetes on the risk of pancreatic cancer was also detected. Compared to non-diabetics with the *ATM* D1853N GG genotype, non-diabetics with the GA/AA, diabetics with the GG, and diabetics with the GA/AA genotypes, respectively, had ORs (95% CI) of 0.96 (0.74-1.24), 1.32 (0.89-1.95), and 3.23 (1.47-7.12) ($P_{interaction} = 0.032$, likelihood ratio test). The OR (95% CI) was 0.91 (0.71-1.17), 1.11 (0.73-1.69), and 2.44 (1.34-4.46) for non-diabetics carrying the *LIG4* CT/TT genotype, diabetics with the CC genotype, and diabetics carrying the CT/TT genotype, respectively, compared to non-diabetics carrying the CC genotype ($P_{interaction} = 0.02$).

Conclusions—These observations suggest that genetic variations in DNA repair may act alone or in concert with other risk factors on modifying a patient's risk for pancreatic cancer.

Keywords

pancreatic cancer; DNA repair; oxidative stress; genetic polymorphisms; single nucleotide polymorphism (SNP)

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Statement of Clinical Relevance: Pancreatic cancer is a highly fatal disease because most of the cases are diagnosed at late stage and the tumors are resistant to most therapies. Early detection for pancreatic cancer is crucial to reduce the mortality. However there is no screening method available to identify the high-risk individuals among those at risk, e.g. cigarette smokers, individuals with diabetes, obesity, and family history of pancreatic cancer. DNA repair plays an important role in cancer susceptibility. The current study has shown that polymorphic variation of DNA repair genes alone or in joint action with diabetes modified the risk of pancreatic cancer. If confirmed by other studies, such information can be used in identification of high-risk individuals for the early detection and primary prevention of pancreatic cancer. Most of genes investigated in this study have previously been shown to affect overall survival of patients with pancreatic cancer. Demonstrating the roles of these genetic variants in the development and in the clinical outcome of this disease will help to understand their functional significance, so novel strategies can be developed to target these genes as an adjuvant therapy for the treatment of pancreatic cancer.

Introduction

Pancreatic cancer is the fourth leading cause of cancer death for both men and women in this country (1). It is a highly aggressive malignancy that shows extensive genomic instability and aneuploidy (2). Identification of genetic factors, environmental exposures, and gene-environment interactions that contribute to pancreatic cancer development is crucial for the primary prevention of this disease.

About 10% of patients with pancreatic cancer have a family history of this disease (3). Some of the familial aggregation can be explained by relation to inherited cancer syndromes, such as familial atypical multiple-mole melanoma, Peutz-Jeghers syndrome, hereditary breast-ovarian cancer, hereditary pancreatitis, familial adenomatous polyposis, and hereditary nonpolyposis colorectal cancer (4,5). Some of the genes that are responsible for these cancer syndromes are involved in DNA repair and cellular response to DNA damage. However, whether these genes contribute to the development of sporadic pancreatic cancer remains unknown. The known and suspected environmental risk factors for sporadic pancreatic cancer include cigarette smoking, obesity, diabetes, chronic pancreatitis, and dietary factors (6-8). The genetic susceptibility factors for sporadic pancreatic cancer have been investigated in a few case-control studies, most of which have examined common gene polymorphisms in carcinogen metabolism (9,10) and DNA repair (11-15). For example, studies conducted by us and by other investigators on DNA repair have shown a significant main effect of *XPF* gene (11), an interaction of *XRCC1* with either *MGMT or APE1* gene (12), or interaction of *XPD* (13), *XRCC1* (12,14), or *XRCC2* gene (15) with cigarette smoking on the risk of pancreatic cancer. These observations support a role of genetic variability in DNA repair in pancreatic cancer and request further investigations on many of the important but unexplored genes involved in various DNA repair pathways.

The base excision repair (BER) and DNA single strand break repair mechanisms are the major repair systems that are involved in the processing of oxidative DNA lesions (16,17). DNA double strand breaks (DSBs) are the most lethal DNA lesions caused by ionizing radiation or some chemical agents. DNA DSBs can also occur as a consequence of DNA replication error. Because DNA DSBs lead to chromosome breaks and genomic instability, many genes involved in the repair of DSBs are well-known tumor suppressors (18,19). We have previously shown that single nucleotide polymorphisms (SNPs) of BER and DSB repair genes, such as *OGG1, XRCC1, APEX1, POLB, ATM, RAD54L* and *RECQL*, were significantly associated with the clinical outcome and overall survival of patients with pancreatic cancer who received chemoradiation (20–22). The relation of some of these genes, such as *XRCC1, XRCC2, XRCC3* and *APEX1*, to the risk of pancreatic cancer has been investigated in our case-control study (12,14). The current study further investigate nine remaining previously clinically investigated SNPs of the *hOGG1, LIG3, LIG4, POLB, ATM, RAD54L*, and *RECQL* genes in a large-scale, case-control study. The main effects of these genes and their potential interactions with smoking, alcohol, and diabetes on the risk of pancreatic cancer were analyzed by logistic regression.

Materials and Methods

Study population

The study design and data collection methods have been previously described in detail (8, 23). Briefly, in this hospital-based case-control study, 734 non-Hispanic white patients with pathologically confirmed primary pancreatic ductal adenocarcinoma and 780 healthy controls were consecutively enrolled at The University of Texas M. D. Anderson Cancer Center from the year 2000 through the year 2007. All study participants were U.S. residents and were able to communicate in English. Control subjects were recruited from healthy spouses, friends, and

non-blood relatives of patients with various types of cancers other than pancreatic cancer, and members of the control group were frequency-matched to cases by age at enrollment (± 5 y), sex, and race. The response rate was 80.6% for cases and 76.9% for controls. Information on cigarette smoking, alcohol consumption, medical history, family history of cancer, and other risk factors was collected by personal interview and a blood sample for genotyping was collected from each participant at the time of enrollment. Cumulative smoking was calculated in pack-years [pack-years = (packs per day) × (years smoked)]. Alcohol consumption was calculated in terms of milliliters of ethanol consumed daily, with 12.0 oz of beer, 4.0 oz of wine, and 1.5 oz of hard liquor each considered to be equivalent to approximately 12.0 ml of ethanol. Family history of cancer among first-degree relatives was collected. Body mass index (BMI, kg/m^2) was calculated based on the self-reported weight and height at age 34 to 39 in 455 cases and 466 controls because this information was collected only after January 2004 in our study. Written informed consent was obtained from each study participant for interview and a blood sample. The study was approved by the Institutional Review Board of M. D. Anderson Cancer Center.

DNA extraction and genotyping

Peripheral blood mononuclear cells were collected from freshly drawn blood by Ficoll-Hypaque (Amersham Pharmacia Biotech, Piscataway, NJ) density gradient centrifugation and stored at -80 °C. DNA was extracted with the use of a FlexiGene DNA kit (Qiagen, Valencia, CA) and a Maxwell16 automated system (Promega, Madison, WI) and stored at 4°C for immediate use.

Genotyping was initially conducted using the Masscode™ technique by BioServe Biotechnologies, Ltd. (Laurel, MD) and later the Taqman diallelic discrimination method in our laboratory. The reference numbers, gene locus, chromosome location, nucleotide change, amino acid change, and minor allele frequency of the SNPs examined in this study are described in Table 1. These SNPs were selected based on their previously reported associations with either risk of cancer or patient survival. All SNPs except *RAD54L* 154C>T and POLB-2133 T>C had a minor allele frequency of > 10% among non-Hispanic whites. Probes and oligonucleotides were obtained from Applied Biosystems (Foster City, CA) using the Assay-by-Design product. The reactions were prepared by using 2× Taqman Universal Master Mix, 40× SNP Genotyping Assay Mix, DNase-free water, and 10 ng genomic DNA in a final volume of 5 μL per reaction. The PCR amplification was done using the ABI Prism 7900 HT sequence-detector (Foster Cite, CA). About 5% of the samples were analyzed in duplicate and 100% consistency was achieved.

Statistical analysis

All statistical analyses were performed using SPSS 15.0 (SPSS Inc., Chicago, IL) and STATA 9.0 (Stata Corp., College Station, TX) software programs. P-values < 0.05 were indicative of statistical significance. The Pearson's chi-square test was used to compare the distribution of categorical variables and genotype frequencies between cases and controls. Odds ratios (ORs) and their associated 95% confidence intervals (95% CIs) were estimated by using an unconditional logistic regression analysis with adjustment for smoking (never, ≤ 20 pack-years, or > 20 pack-years), alcohol (never, ≤ 60 ml of ethanol/day, or > 60 ml of ethanol/day), diabetes (yes or no), and family history of cancer among first-degree relatives (yes or no). Because diabetes could be a manifestation of pancreatic cancer, individuals with recent diabetes onset, i.e. within 2 years before the cancer diagnosis for cases and before recruitment to the study for controls were excluded from some of the analyses. Because information on BMI was missing from study participants recruited in the early stage of the investigation, BMI was not included in the multivariate model. For detection of possible interactions between genotypes and smoking, alcohol, diabetes or BMI, individuals without the risk factor (e.g. never smoked) and

the non-at-risk genotype were used as the reference group and adjusted ORs for never smokers with the at-risk genotype (OR_{10}), smokers with non-at-risk genotype (OR_{01}), and smokers with the at-risk genotype (OR_{11}) were estimated using unconditional logistic regression. An OR_{11} greater than the sum of $OR_{10} + OR_{01}$ or greater than the product of $OR_{10} \times OR_{01}$ indicates a more than additive or more than multiplicative effect, respectively. The cross-product term of genotype with smoking, alcohol, diabetes and BMI was generated with the use of the logistic regression model correspondingly. The significance of the interaction term was tested by using a likelihood ratio test, with the full model containing the interaction term, the main effect of the genotype, and the exposure variable and reduced model lacking the interaction term. For any statistically significant association we observed, we estimated the false-positive report probability (FPRP) using the methods described by Wacholder et al. (24). The FPRP value for noteworthiness was set as 0.2.

Results

Characteristics of the study subjects

The distribution of demographics, risk factors, and genotypes between cases and controls are described in Table 2. The mean ± standard deviation ages of cases and controls were 62.2 ± 9.6 and 62.0 ± 9.6 years, respectively ($P = 0.673$). The cases and controls were well matched by age and sex. As previously described (23,25), history of diabetes, family history of cancer, heavy smoking, heavy alcohol drinking and overweight were all associated with increased risk of pancreatic cancer in this study population.

Main effect of genotype

The nine SNPs were successfully amplified in 95.8% to 99.1% of the patients and controls. All SNPs except one, *OGG1* T2657C ($\chi^2 = 6.73$, $P < 0.05$), followed the Hardy-Weinberg equilibrium in both cases and controls (data not shown). There were no statistically significant differences in genotype distributions between cases and controls for seven out of the nine SNPs (Table 3). The *LIG3* G-39A AA homozygous mutant was associated with a significantly reduced risk of pancreatic cancer (OR, 0.23; 95% CI, 0.06-0.82; $P = 0.024$) after adjusting for age, sex, smoking, alcohol, diabetes, and family history of cancer. On the other hand, *ATM* D1853N AA variant was significantly associated with an increased risk of pancreatic cancer (OR, 2.55; 95% CI, 1.08-6.00; $P = 0.032$), with adjustment for other confounders. The estimated FPRP was 0.136 for *LIG3* G-39A and 0.166 for *ATM* D1853N, given a prior probability of 25%. Both are below the threshold of 0.20 indicating noteworthiness.

Interaction of genotype with known risk factors

Next, we examined the potential interactions between genotype and known risk factor for pancreatic cancer in this study population, such as cigarette smoking, alcohol intake, diabetes, and BMI. Because of the low frequency of the homozygous variants, they were combined with the heterozygous group in this analysis. The exposure variables used were: never smoker versus ever smoker; non-drinker and light drinker (<60 ml/day) versus heavy drinker (>60 ml/day); diabetes (no versus yes); and BMI (≤25 versus >25 kg/m^2). As shown in Table 4, there were no significant interactions of genotypes with smoking, alcohol, and BMI. There was a borderline significant interaction of *POLB* T-2133C genotype with smoking ($P_{interaction} = 0.051$). A statistically significant interaction of *ATM* D1853N or *LIG4* C54T genotype with diabetes was observed in the analysis excluding recent onset diabetes. For example, when the group of non-diabetics with the *ATM* D1853N GG genotype was compared to other groups, ORs (95% CI) of 0.96 (0.74-1.24), 1.32 (0.89-1.95), and 3.23 (1.47-7.12) were obtained for non-diabetics with the GA/AA, diabetics with the GG, and diabetics with the GA/AA genotypes, respectively ($P_{\text{interaction}} = 0.032$). The OR (95% CI) was 0.91 (0.71-1.17), 1.11 (0.73-1.69), and 2.44 (1.34-4.46) for non-diabetics carrying the *LIG4* CT/TT genotype,

diabetics with the CC genotype, and diabetics carrying the CT/TT genotype, respectively, compared to non-diabetics carrying the CC genotype ($P_{interaction}$= 0.02). A weak interaction of the *OGG1* T2657C genotype with diabetes was observed, $P_{interaction}$ = 0.049. However, this interaction became statistically non-significant ($P_{interaction}$ = 0.076) after excluding individuals with recent onset diabetes. *RECQL* A159C and *RAD54L* C154T genotype also showed a non-significant interaction with diabetes when all study participants were included in the analysis.

Discussion

In this large case-control study, we examined SNPs of a number of DNA repair genes in association with risk of pancreatic adenocarcinoma. We observed a significant main effect of the homozygous variants of the *LIG3* G-39A and *ATM* D1853N genotypes, and a statistically significant interaction of the *ATM* D1853N and *LIG4* C54T genotype with diabetes on the risk of pancreatic cancer. These findings support our hypothesis that genetic variations in DNA repair modify the risk of pancreatic cancer.

DNA joining enzymes play an essential role in the maintenance of genomic integrity and stability. Three mammalian genes encoding DNA ligases, *LIG1*, *LIG3*, and *LIG4*, have been identified and each has distinct functional significance. *LIG3* participates in BER and DNA singles strand break repair by forming a stable complex with XRCC1. The *LIG3* haplotype has been associated with radiation sensitivity in a study of breast cancer patients (26). *LIG3* SNPs have been associated with increased risk of lung cancer (27) and esophageal cancer (28), but no association was found in other studies of cancer of the lung (29,30), bladder (31), colon (32), and breast (33). The current study is the first to show a significant protective effect of the *LIG3* G-39A AA genotype on risk of pancreatic cancer. However, this SNP is located in the intron region of the gene and the functional significance of this genetic variation is unknown. The frequency of the homozygous variant is very low so the observed association could be by chance alone. Whether this SNP is in linkage with other functionally significant SNPs of the gene needs further investigation. LIG4 is essential for V(D)J recombination and DNA double-strand break (DSB) repair through nonhomologous end joining (NHEJ). Polymorphisms of this gene have been related to significantly increased risk of developing glioma (34), multiple myeloma (35) and lymphoblastic leukemia (36), as well as to the survival of patients with breast cancer (37). The *LIG4* C54T SNP that showed a significant interaction with diabetes in modifying the risk of pancreatic cancer in the current study is located at 3′UTR. Although DNA sequences in this region do not translate into proteins, the 3′UTR may contain sequence motifs crucial for the regulation of transcription, mRNA stability, and cellular location of the mRNA or the binding of microRNA (38). It is conceivable that *LIG4* gene variant may confer a deficient repair of DNA damage caused by diabetes-associated elevated level of oxidative stress, in turn increase the risk of pancreatic cancer.

ATM is an important cell cycle checkpoint kinase that plays a critical role in cellular response to DNA damage and in maintaining genome stability. Germline mutations in the *ATM* gene result in the rare genomic instability syndrome ataxia telangiectasia (AT), which is characterized by elevated cancer risk. AT heterozygote or common SNPs of the *ATM* gene have been associated with increased risk of developing breast cancer (39-41). In the current study we have shown a significant main effect of the *ATM* D1853N homozygous variant on increased risk of pancreatic cancer. The same SNP was previously associated with increased risk of second primary tumors among breast cancer patients (42). Because the homozygous variant AA genotype had a very low frequency (1% in the controls); the possibility that its association with increased risk of pancreatic cancer was due to chance alone cannot be excluded. Notably, a possible synergistic effect of this SNP with diabetes was also observed in this study population. The OR of pancreatic cancer was 4.17 for diabetics carrying the A allele versus 2.08 for diabetics carrying the G allele compared with non-diabetics. Because

diabetes could be a manifest of pancreatic cancer, we performed analysis among those with a greater than 2 years of diabetes duration to reduce the problem of reversal causality; and the interaction of *ATM* D1853N genotype with diabetes remained statistically significant. It is conceivable that diabetes increases oxidative stress and deficiency in the defending DNA repair genes would confer a greater chance for tumor development via impaired cellular response to accumulative DNA damage.

The *OGG1* gene is a BER gene that removes an oxidative DNA lesion, such as 7,8-dihydro-8-oxo-guanine (8oxoG), from DNA. Because 8oxoG leads to a high degree of DNA mispairing, decreased OGG1 activity could lead to a higher frequency of mutation and could possibly increase the cancer risk of an individual under oxidative stress. Among the numerous DNA repair genes that have been investigated in cancer studies, the OGG1 genotype has been frequently associated with altered risk of human cancers (43,44). We have previously observed a significantly reduced overall survival time for patients carrying the *OGG1* C-315G (aka S326C) GG homozygous variant genotype (22). The current study observed a weak interaction of the *OGG1* C-315G CC/CG genotype with diabetes in increased risk of pancreatic cancer. Together these observations suggest that the CC/CG genotype may confer relatively little enzyme activity, thus causing an increased risk of pancreatic cancer. However, neither the cancer association nor the functional significance of the *OGG1* genotype is conclusive (43, 44). Furthermore, our observations need to be replicated in other study populations.

Our study has several merits as well as limitations. Except *OGG1* (12), none of the genes investigated in the current study has previously been examined in association with risk of pancreatic cancer. We for the first time demonstrated a possible role of genes involved in the repair of DNA strand breaks (*LIG3* and *LIG4*) or in cellular response to DNA damage (*ATM*) in modifying the risk of pancreatic cancer. Although the current study has a relatively large sample size, the power to detect the main genotype effect in low-frequency homozygous mutants and the interaction of genotype with other risk factors is still limited. So the possibility that some of the observations were false discoveries associated with multiple testing can not be excluded. In addition, the study was conducted in a single tertiary referral hospital; results from this study population may not be generalized to the U.S. population. Some of the genes investigated in this study have previously been associated with patient survival, the association of genotype and risk of pancreatic cancer could be biased if our study missed a lot of patients that were succumbed to this fatal disease rapidly. We also admit that the number of genes and SNPs selected were very limited and the functional significance of the SNPs was largely unknown. We may have missed many important genes and SNPs on the same DNA repair pathways. Future large studies with systematic selection of genes and SNPs are required to provide sufficient power to reveal the true associations between the rare variant genotypes and the risk of pancreatic cancer.

Acknowledgements

We thank all the personnel involved in patient recruitment and data collection. We thank Ms. Kathryn B. Carnes and Sue Moreau for editing the manuscript.

Grant support: National Institutes of Health (NIH) grants CA98380 (to D.L.) and CA101936 (to J.L.A.), National Institute of Environmental Health Sciences Center grant P30 ES07784, NIH core grant CA16672, and the Lockton Pancreatic Cancer Research Funds (to D.L.).

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Table 1

Characteristics of examined SNPs

Gene	chromosome	SNP	RS#	MAF
LIG3	17q11.2-q12	IVS18-39 G>A	2074522	0.104
LIG4	13q33-q34	Ex3+54 C>T, 3′UTR	1805388	0.137
OGG1	3p26.2	IVS7+2657 T>C	293794	0.160
		Ex6-315 C>G, S326C	1052133	0.225
ATM	11q22-q23	IVS20-77C>T	664677	0.711
		Ex37 +61G>A, D1853N	1801516	0.161
RAD54L	1p32	Ex18+157C>T, A730A	1048771	0.123
POLB	8p11.2	IVS2-2133 T>C	2953993	0.789
RECQL	12p12	Ex15+159 A>C, 3′UTR	13035	0.275

Abbreviations: RS#, SNP reference number; MAF, minor allele frequency.

Allele frequencies obtained from NCI SNP500 cancer database and NCBI database.

Table 2

Distribution of selected variables among cases and controls

Variable	Cases (n=734)		Controls (n=780)		*P* value (x^2)
	N	(%)	N	(%)	
Age at recruitment (y)					0.899
≤ 50	89	(12.1)	95	(12.2)	
51-60	209	(28.5)	235	(30.1)	
61-70	285	(38.8)	291	(37.3)	
> 70	151	(20.6)	159	(20.4)	
Gender					0.332
Female	286	(39.0)	323	(41.4)	
Male	448	(61.0)	457	(58.6)	
Family history of Cancer[a]					0.001
No	272	(37.1)	357	(45.8)	
Yes	461	(62.9)	423	(54.2)	
History of diabetes					<0.001
No	540	(73.6)	680	(87.2)	
Yes	194	(26.4)	100	(12.8)	
Smoking status					0.002
Non-smokers	292	(39.8)	369	(47.3)	
≤ 20 pack years	173	(23.6)	187	(24.0)	
> 20 pack years	269	(36.6)	224	(28.7)	
Alcohol consumption					0.049
Never	305	(41.6)	338	(43.3)	
≤ 60 ml/day	342	(46.6)	379	(48.6)	
> 60 ml/day	87	(11.9)	63	(8.1)	
Body mass index[b]					
< 25 kg/m^2	236	(52.2)	288	(62.1)	
≥ 25 kg/m^2	216	(47.8)	176	(37.9)	0.003

[a] Information was missing from one patient because of adopted family.

[b] Information was available for only 452 cases and 464 controls.

Table 3

Genotype distribution between cases and controls

Genotype	Cases (n=734)		Controls (n=780)		OR (95% CI)[a]	*P* value
	N	(%)	N	(%)		
***LIG3* G-39A**						
GG	585	(80.7)	632	(81.4)	1.0	
AG	137	(18.9)	132	(17.0)	1.13 (0.86-1.48)	0.361
AA	3	(0.4)	12	(1.5)	0.25 (0.07-0.90)	0.034
***LIG4* C54T**						
CC	503	(69.6)	539	(69.5)	1.0	
CT	197	(27.2)	208	(26.8)	0.97 (0.77-1.23)	0.809
TT	23	(3.1)	29	(3.7)	0.86 (0.49-1.53)	0.617
***OGG1* T2657C**						
TT	487	(67.4)	502	(64.6)	1.0	
TC	198	(27.4)	232	(29.9)	0.90 (0.72-1.14)	0.399
CC	38	(5.3)	43	(5.5)	0.92 (0.58-1.47)	0.729
***OGG1* C-315G**						
CC	413	(57.2)	461	(59.6)	1.0	
CG	276	(38.2)	271	(35.1)	1.14 (0.92-1.42)	0.228
GG	33	(4.6)	41	(5.3)	0.83 (0.51-1.36)	0.461
***ATM* C-77T**						
TT	264	(36.5)	243	(32.3)	1.0	
CT	341	(47.2)	378	(50.3)	0.85 (0.67-1.07)	0.157
CC	118	(16.3)	131	(17.4)	0.80 (0.58-1.09)	0.155
***ATM* D1853N**						
GG	524	(72.0)	565	(73.1)	1.0	
GA	186	(25.5)	200	(25.9)	1.01 (0.80-1.28)	0.924
AA	18	(2.5)	8	(1.0)	2.76 (1.18-6.46)	0.019
***POLB* T-2133C**						
CC	614	(84.9)	653	(84.1)	1.0	
CT	106	(14.7)	120	(15.5)	0.76 (0.48-1.20)	0.237
TT	3	(0.4)	3	(0.4)	1.28 (0.37-4.45)	0.696
***RECQL* A159C**						
AA	238	(33.7)	252	(33.8)	1.0	

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Genotype	Cases (n=734)		Controls (n=780)		OR (95% CI)[a]	*P* value
	N	(%)	N	(%)		
AC	325	(46.0)	341	(45.8)	0.98 (0.77-1.25)	0.902
CC	143	(20.3)	152	(20.4)	1.01 (0.75-1.36)	0.961
***RAD54L* C154T**						
CC	579	(79.4)	599	(77.6)	1.0	
CT	140	(19.2)	157	(20.3)	0.92 (0.71-1.19)	0.528
TT	10	(1.4)	16	(2.1)	0.61 (0.27-1.40)	0.242

[a]OR was adjusted for smoking, alcohol, diabetes, and family history of cancer.

Table 4

Interaction of genotype with other risk factors for pancreatic cancer (OR (95% CI))

Genotype	Exposure	Smoking [a]	Alcohol [b]	Diabetes [c]	Diabetes [d]	BMI [e]
***LIG3* G-39A**						
GG	(-)	1.00	1.00	1.00	1.00	1.00
AG&AA	(-)	1.12 (0.76-1.65)	1.05 (0.79-1.39)	1.09 (0.81-1.47)	1.09 (0.81-1.46)	0.89 (0.56-1.42)
GG	(+)	1.29 (1.01-1.64)	1.32 (0.89-1.96)	2.50 (1.84-3.39)	1.58 (1.08-2.33)	1.52 (1.10-2.10)
AG&AA	(+)	1.31 (0.90-1.91)	1.59 (0.72-3.54)	2.38 (1.38-4.10)	1.38 (0.65-2.91)	1.22 (0.73-2.02)
$P_{interaction}$ [f]		0.73	0.73	0.69	0.59	0.76
***LIG4* C54T**						
CC	(-)	1.00	1.00	1.00	1.00	1.00
CT&TT	(-)	0.95 (0.67-1.33)	0.94 (0.74-1.19)	0.91 (0.71-1.17)	0.91 (0.71-1.17)	0.95 (0.64-1.41)
CC	(+)	1.24 (0.96-1.61)	1.31 (0.85-2.02)	2.17 (1.56-3.01)	1.11 (0.73-1.69)	1.48 (1.06-2.08)
CT&TT	(+)	1.22 (0.88-1.67)	1.41 (0.76-2.62)	2.69 (1.71-4.25)	2.44 (1.34-4.46)	1.41 (0.90-2.23)
$P_{interaction}$		0.88	0.68	0.29	0.02	1.00
***OGG1* T2657C**						
TT	(-)	1.00	1.00	1.00	1.00	1.00
CT&CC	(-)	0.93 (0.67-1.30)	0.95 (0.75-1.19)	0.82 (0.64-1.04)	0.82 (0.64-1.04)	0.99 (0.68-1.44)
TT	(+)	1.28 (0.98-1.67)	1.60 (1.02-2.49)	1.99 (1.43-2.76)	1.20 (0.79-1.82)	1.55 (1.09-2.19)
CT&CC	(+)	1.13 (0.83-1.54)	0.96 (0.54-1.74)	2.92 (1.82-4.68)	1.89 (1.04-3.44)	1.35 (0.87-2.08)
$P_{interaction}$		0.81	0.21	0.049	0.076	0.66
***OGG1* C-315G**						
CC	(-)	1.00	1.00	1.00	1.00	1.00
CG&GG	(-)	1.02 (0.74-1.40)	1.09 (0.87-1.36)	1.12 (0.89-1.41)	1.12 (0.88-1.41)	1.22 (0.85-1.75)
CC	(+)	1.20 (0.90-1.59)	1.30 (0.83-2.06)	2.57 (1.80-3.69)	1.78 (1.11-2.86)	1.60 (1.11-2.32)
CG&GG	(+)	1.38 (1.02-1.88)	1.58 (0.90-2.78)	2.55 (1.69-3.83)	1.40 (0.85-2.32)	1.60 (1.06-2.40)
$P_{interaction}$		0.60	0.73	0.66	0.32	0.47
***ATM* C-77T**						
TT	(-)	1.00	1.00	1.00	1.00	1.00
CC&CT	(-)	0.73 (0.52-1.01)	0.85 (0.67-1.07)	0.81 (0.64-1.03)	0.81 (0.64-1.03)	0.71 (0.49-1.04)
TT	(+)	1.13 (0.78-1.63)	1.47 (0.82-2.65)	2.25 (1.41-3.60)	1.25 (0.71-2.20)	1.23 (0.77-1.97)
CC&CT	(+)	1.03 (0.75-1.43)	1.01 (0.63-1.63)	2.06 (1.43-2.96)	1.37 (0.86-2.16)	1.14 (0.75-1.71)

Genotype	Exposure	Smoking [a]	Alcohol [b]	Diabetes [c]	Diabetes [d]	BMI [e]
$P_{interaction}$		0.30	0.51	0.68	0.40	0.38
***ATM* D1853N**						
GG	(-)	1.00	1.00	1.00	1.00	1.00
GA/AA	(-)	1.03 (0.72-1.45)	1.12 (0.88-1.44)	0.96 (0.74-1.24)	0.96 (0.74-1.24)	1.50 (1.01-2.22)
GG	(+)	1.24 (0.96-1.60)	1.52 (0.98-2.34)	2.08 (1.52-2.84)	1.32 (0.89-1.95)	1.64 (1.17-2.30)
GA/AA	(+)	1.40 (1.00-1.96)	1.17 (0.63-2.18)	4.17 (2.41-7.22)	3.23 (1.47-7.12)	1.89 (1.19-3.01)
$P_{interaction}$		0.69	0.35	0.022	0.032	0.41
***POLB* T-2133C**						
CC	(-)	1.00	1.00	1.00	1.00	1.00
CT&TT	(-)	0.65 (0.41-1.01)	0.91 (0.68-1.24)	0.84 (0.61-1.16)	0.84 (0.61-1.15)	0.83 (0.52-1.33)
CC	(+)	1.15 (0.91-1.46)	1.38 (0.93-2.03)	2.28 (1.69-3.07)	1.32 (0.90-1.93)	1.41 (1.03-1.93)
CT&TT	(+)	1.33 (0.90-1.98)	1.15 (0.47-2.84)	2.83 (1.52-5.27)	2.38 (1.05-5.39)	1.67 (0.92-3.03)
$P_{interaction}$		0.051	0.88	0.29	0.101	0.36
***RECQL* A159C**						
AC&CC	(-)	1.00	1.00	1.00	1.00	1.00
AA	(-)	0.87 (0.61-1.23)	1.01 (0.80-1.28)	0.93 (0.72-1.19)	0.93 (0.73-1.19)	1.07 (0.73-1.55)
AC&CC	(+)	1.20 (0.92-1.58)	1.27 (0.81-1.99)	2.06 (1.47-2.88)	1.38 (0.91-2.11)	1.51 (1.05-2.15)
AA	(+)	1.36 (1.00-1.86)	1.28 (0.70-2.33)	3.20 (1.96-5.20)	1.64 (0.88-3.05)	1.48 (0.94-2.31)
$P_{interaction}$		0.24	0.96	0.092	0.57	0.78
***RAD54* C154T**						
CC	(-)	1.00	1.00	1.00	1.00	1.00
CT/TT	(-)	0.73 (0.50-1.07)	0.94 (0.72-1.23)	1.01 (0.76-1.33)	1.00 (0.76-1.33)	0.87 (0.57-1.32)
CC	(+)	1.15 (0.90-1.48)	1.57 (1.03-2.39)	2.89 (2.10-3.98)	1.74 (1.16-2.60)	1.64 (1.17-2.28)
CT/TT	(+)	1.22 (0.85-1.74)	0.89 (0.44-1.79)	1.59 (0.97-2.64)	1.26 (0.67-2.37)	0.95 (0.58-1.57)
$P_{interaction}$		0.16	0.21	0.063	0.42	0.23

All models included age, sex, smoking, alcohol, diabetes, and family history of cancer, when appropriate.

[a] Smoking: never vs. ever

[b] Alcohol: 0-60 ml/day vs. >60 ml/day

[c] Diabetes: no vs. yes

[d] Diabetes after exclusion of recent onset diabetes: no vs. yes

[e] BMI: body mass index (kg/m^2): <25 vs. ≥25

[f] P for interaction, likelihood ratio test