Published in final edited form as:
Cancer Epidemiol Biomarkers Prev. 2010 January ; 19(1): 251–257. doi:10.1158/1055-9965.EPI-09-0629.

Association of Mitotic Regulation Pathway Polymorphisms with Pancreatic Cancer Risk and Outcome

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Abstract

Background—Mitosis is a highly regulated process that serves to ensure the fidelity of cell division. Disruption of mitotic regulators leading to aneuploidy and polyploidy is commonly observed in cancer cells. Single nucleotide polymorphisms (SNPs) in regulators of mitosis may promote chromosome mis-segregation and influence pancreatic cancer and/or survival.

Methods—Thirty four SNPs, previously associated with breast cancer risk, from 33 genes involved in regulation of mitosis, were investigated for associations with pancreatic cancer risk in 1,143 Caucasian patients with pancreatic adenocarcinoma and 1,097 unaffected controls from the Mayo Clinic. Associations with survival from pancreatic cancer were also assessed using 1,030 pancreatic cancer cases with known outcome.

Results—Two SNPs in the *APC* (rs2431238) and *NIN* (rs10145182) loci, out of 34 examined, were significantly associated with pancreatic cancer risk (p=0.035 and p=0.038, respectively). Further analyses of individuals categorized by smoking and BMI identified several SNPs displaying significant associations (p<0.05) with pancreatic cancer risk, including *APC* rs2431238 in individuals with high body mass index (BMI≥30) (p=0.031) and *NIN* rs10145182 in ever smokers (p=0.01). In addition, survival analyses detected significant associations between SNPs in *EIF3S10* and overall survival (p=0.009), SNPs from five genes and survival in resected cancer cases (p<0.05), and SNPs from two other genes (p<0.05) and survival of locally advanced cancer cases.

Conclusion—Common variation in genes encoding regulators of mitosis may independently influence pancreatic cancer susceptibility and survival.

Keywords

Mitosis; association; SNPs; survival

Introduction

Pancreatic cancer is a common cancer with an overall five-year survival rate of less than 5%. It has been estimated that 10–20% of pancreatic cancers arise due to a significant inherited component (1). Mutations in moderately penetrant susceptibility genes such as *BRCA2* (2), *CDKN2A* (Familial atypical melanoma mole syndrome) (3) and *MLH1* (hereditary nonpolyposis colon cancer) (4) account for less than 5% of all pancreatic cancers. This suggests

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that much of the inherited risk of pancreatic cancer may be due to low penetrance, common genetic variants.

Chromosomal instability, aneuploidy and polyploidy are common features of many tumors including breast (5) and exocrine pancreas (6,7). These defects in chromosome number arise through several different mechanisms involving either mis-segregation of chromosomes or failure of cell division. Mitotic kinases control and regulate all phases of mitosis including entry, progression and exit (8). They phosphorylate a large number of structural and regulatory proteins involved in centrosome duplication and separation, chromosome condensation, spindle assembly and fidelity, chromosome segregation, and cytokinesis to ensure successful cell division. Altered expression of several kinases, including members of the Aurora, PLK and NEK families, are known to induce centrosome amplification, chromosome missegregation and failure of cytokinesis leading to chromosomal instability (9-11). Similarly, a recent high-throughput RNAi screen of kinases in Drosophila identified a number of these proteins that are required for normal cell division (12). Other functional screens have identified additional structural and regulatory proteins that are necessary for cell division (13).

The integrity of the centrosome, the primary microtubule organizing center of the cell, is also required for normal cell division. The centrosome maintains cellular polarity, is required for entry into S-phase, and mediates the process of chromosome segregation. Numerical and functional defects of the centrosome, that can result in improper chromosome segregation through multipolar or monopolar mitoses, are common in many cancers (14-17).

Given the frequent involvement of aneuploidy and polyploidy in *in situ* and invasive tumors, and evidence in support of a direct role for chromosomal instability in predisposition to cancer, we hypothesized that commonly inherited genetic variation in mitotic regulators predispose to cancer. To explore this hypothesis we evaluated associations between tagging SNPs ($r^2>0.8$) from over 200 genes encoding proteins implicated in the mitotic process in breast cancer cases and unaffected controls from the Mayo Clinic Breast Cancer Study. We identified 34 SNPs from 33 genes that displayed significant associations with breast cancer risk ($p<0.01$) (18, 19). Here, we further evaluated the contribution of SNPs in mitotic regulators to cancer by assessing associations between these 34 SNPs and pancreatic cancer risk in a rapid ascertainment clinic-based study of 1,143 pancreatic cancer cases and 1,097 unaffected controls from the Mayo Clinic. In addition, we extended our studies to investigate the influence of these studies on survival of pancreatic cancer patients.

Materials and Methods

Pancreatic cancer case-control study

From October 2000 through March 2007, patients with pancreatic adenocarcinoma were consecutively recruited under an ultra-rapid recruitment protocol (recruitment at the time of clinic visit for the initial work up for pancreatic cancer) to a registry during their visit to the Mayo Clinic. Of those approached, 71% consented to participate in the study. A total of 1,203 individuals with pancreatic adenocarcinoma with self-completed risk factor questionnaires, family cancer history information and available blood samples for DNA analysis, representing 62% of all pancreatic adenocarcinoma patients identified at Mayo Clinic during this time period, were selected for genotyping. The median time from initial diagnosis to enrollment on the study was 14 days (25%-75% 2-40 days). The median/mean age at diagnosis for all pancreas adenocarcinoma cases at Mayo Clinic over the same time period was 66/65.6 years, versus 67/65.5 for cases included in this study.

Stage of disease at surgery was abstracted from the medical record and categorized as resected, locally advanced, metastatic and not specified. The resected category included patients

undergoing a tumor resection (whipple, distal pancreatectomy, total pancreatectomy). Patients with localized disease that were not resected were categorized as locally advanced. When grouping study cases by stage, 29% were resected, 33% locally advanced, and 38% metastatic. In contrast, when grouping all pancreatic cancer cases at Mayo Clinic during the same time period, 24% were resected, 33.5% were locally advanced, and 42.5% metastatic. Thus, a slightly higher proportion of patients undergoing surgery participated in the study. Overall, the participating cases were representative of the overall Mayo Clinic pancreatic adenocarcinoma patient population.

From May 2004 to February 2007, healthy controls were recruited from the General Internal Medicine clinic at Mayo Clinic (Rochester) (20). Peripheral blood was collected for DNA analysis and self-completed risk factor questionnaires were administered. For this study, 1,203 controls frequency matched to cases on gender, residence (three-state (MN, WI, IA); five state area (MN, WI, IA, SD, ND); or outside of area), age at recruitment (in 5-year increments), and race/ethnicity were selected.

Study participants provided information about age at initiation and cessation of smoking and the number of packs smoked per day in the self-completed questionnaire. Alternatively, smoking information was extracted from the medical record of 24% of controls and 23% of cases. Smoking data were available for 99.7% of study participants. Subjects were categorized as “never smokers” and “ever smokers” (≥100 cigarettes in their lifetime). Ever smokers were further stratified by current and former smoking status and by number of pack-years of smoking (≤20 pack-years, >20-40 pack-years, and >40 pack-years). Self reported BMI prior to onset of disease symptoms was obtained from the risk factor questionnaires and subjects were categorized by as BMI <30 or BMI ≥30.

Overall survival data was obtained from the medical record death certificates, online resources (Accurint), and direct contact with next of kin. The median survival time was 271 days. This study was approved by the Mayo Clinic Institutional Review Board.

Retrospective cohort survival study

Cases alone were used in survival analyses for each SNP, using date of pancreatic cancer diagnosis to date of last follow up or death. Stage of disease at surgery was abstracted from the medical record and categorized as resected, locally advanced, metastatic and not specified. Overall survival data was obtained from the medical record at the Mayo Clinic and external sites, death certificates, online resources (Accurint), and direct contact with next of kin. This study was approved by the Mayo Clinic Institutional Review Board.

Genotyping

TagSNPs from genes encoding proteins required for normal cell division or implicated in centrosome structure and function proteins that were significantly associated with risk of breast cancer ($p<0.01$) in a breast cancer case-control study, were selected for analysis. DNA samples were extracted from blood provided by both cases and controls. All DNA samples were genotyped for the 34 SNPs in the Mayo Clinic Genotyping Shared Resource on an Illumina Golden Gate® Custom 768-plex OPA panel as part of a larger study using the standard protocol. Genotyping was successful for 1,189 cases (1,143 Caucasian) and 1,126 controls (1,097 Caucasian) with average SNP call rate and sample success rates >99%. Forty-seven duplicate pairs displayed 99.9% concordance.

Statistical Analysis

Cases and controls were similar in age but differed in BMI, sex (despite attempted frequency-matching), percent of ever-smokers and percent reporting a first degree relative with pancreatic

cancer, as shown in Table 1. All SNPs were in Hardy-Weinberg equilibrium (p>0.05) in controls. The association between each SNP and disease was assessed using unconditional logistic regression under a log-additive model in SAS (SAS software, version 9.1.2, Cary, North Carolina). Multivariate logistic regression analyses adjusted for age, gender, smoking status (ever/never), family history of pancreas cancer in a first degree relative (yes/no), and body mass index (BMI) were also performed. In addition, analyses were conducted following stratification of cases and controls by gender and extent of smoking (ever/never and pack-years). Associations with overall survival (based on date of diagnosis to date of death) were assessed using a Cox proportional hazards model adjusted for age at diagnosis, gender and pancreatic cancer status (resected, locally advanced and metastatic). These analyses were adjusted for multiple testing using a Bonferroni correction.

Results and Discussion

Two of 34 candidate SNPs from genes that regulate normal cell division displayed significant associations (p<0.05) with pancreatic cancer risk under a log-additive model. Results from tests for association are shown in Table 2. *APC* rs2431238 was associated with an increased risk of pancreatic cancer (OR, 1.14; 95%CI, 1.01-1.30; p=0.035), whereas *NIN* rs10145182 was associated with a reduced risk of pancreatic cancer (OR, 0.88; 95%CI, 0.78-0.99; p=0.038). None of the other 32 SNPs displayed significant associations with pancreatic cancer risk. Analyses were repeated using a multivariate model in which ORs were adjusted for age at diagnosis or consent, sex, ever/never smoking, BMI and family history of pancreatic cancer. The effects of these SNPs on risk were not substantially altered when accounting for these covariates (Table 2).

Given that BMI is an established risk factor for pancreatic cancer with incidence of pancreatic cancer increasing with increased BMI (21), we also evaluated associations between the SNPs and pancreatic cancer risk in individuals with high BMI (≥30) and lower BMI (<30). Five SNPs in the *PRC, PRKCA, TEX14, YPEL2*, and *APC* genes displayed significantly increased risk in the high BMI category, whereas two SNPs in *MCPH1* and *MAP2K1* were associated with risk in the low BMI category (Table 3,Supplemental Table 1). In addition, because smoking, a major source of carcinogen exposure, is an established risk factor for pancreatic cancer (22), we considered the influence of the SNPs on risk in smokers and non-smokers. An increased risk of cancer in non-smokers was observed for rs12209182 in *RIPK1*, an activator of NFκB associated apoptosis (OR, 1.22; p=0.027), and rs4579555 in *RAD21*, a gene encoding a DNA repair protein (OR, 1.50; p=0.003). This is consistent with a model, in which the SNPs inhibit the apoptotic and DNA repair signaling by these proteins and promote accumulation of mutations and onset of pancreatic cancer. In contrast, the SNP in *NIN*, that displayed significance overall, was associated with risk in ever and former smokers. Similar associations were observed for SNPs in *MCPH1* and *PRKCA*. No evidence of increasing significance or effect size in response to increasing levels of smoking was observed, other than a significant association for a SNP in *FYN* in individuals in the highest category of smoking (pack-years >=40) (Supplemental Table 1). Overall, none of these associations retained significance after adjustment for multiple testing.

Few studies of candidate genetic modifiers of survival in pancreatic cancer cases have been conducted to date. Here we took advantage of the availability of detailed outcome data in the Mayo Clinic medical records for the cases in the Mayo Clinic case-control study to assess the influence of the 34 selected SNPs on overall survival among the pancreatic cancer cases (Supplemental Table 2). A total of 1,030 cases were assessed as a group and also subcategorized as resected (n=304), locally advanced (n=347), and metastatic (n=379) cancers. Analyses showed that the minor allele of rs10787899 in *EIF3S10* was highly significantly associated with decreased overall survival (HR, 1.22; p=0.009) (Table 4). In addition, restricting to

resected cases found that SNPs in *AXIN2* (p=0.005), *TEX14*, (p=0.017), *TUBG1* (p=0.026), *KIAA0999* (p=0.022) and *GSPM2* (p=0.006) were associated with survival (Table 4). Likewise, rs2431238 in *APC* (p=0.017) and rs2245092 in *TLK2* (p=0.027) were associated with survival in locally advanced patients (Table 4). No specific associations with metastatic cancer were observed. Treatment data were not included in these analyses because detailed information was available on only a minority of patients and because treatment arguably does not have a large impact upon survival in pancreatic cancer.

Interestingly, none of the SNPs displayed significant associations with both overall survival and the specific subgroups of resected or locally advanced cancers. However, the finding that rs11079571 in *AXIN2* and rs2431238 in *APC* were associated with survival in resected and locally advanced cancer patients, respectively, was of interest because these genes encode important components of the β-catenin destruction complex. This complex mediates Wnt signaling and regulates the level of the β-catenin transcription factor in the cytoplasm and in the nucleus. Activation of the Wnt/β-catenin signaling cascade as a result of genetic changes in *APC*, *AXIN2* and *AXIN1* has been implicated in several types of human cancers (23-25), with most mutations reported in sporadic colorectal cancers and germline DNA of colorectal cancer patients (23,25). Critical serine/threonine residues at the N-terminus of β-catenin that affect the stability of the protein are mutated in a wide variety of human tumors including pancreatic cancers (26). Furthermore, more than 65% of pancreatic tumors display increased β-catenin expression, consistent with enhanced membranous, cytoplasmic, and nuclear localization of the protein (27). In addition, altered catenin levels are strongly correlated with poor survival of pancreatic cancer patients (28). Further studies are needed to determine whether SNPs in the β-catenin destruction complex genes regulate β-catenin levels and outcome in pancreatic cancer.

It was also noted that most of the SNPs associated with risk and survival in this study were located in genes encoding components of the centrosome. As mentioned above, numerical and functional defects of the centrosome, that are common in many cancers, have been implicated in enhanced proliferation and induction of aneuploidy and polyploidy in tumor cells, and tumor aggressiveness (11,14,29). Thus, our findings suggest that common genetic variation in centrosome components may influence patient survival.

In summary, we evaluated a series of candidate SNPs from genes involved in regulation of cell division in a large rapidly ascertained pancreatic cancer case-control study and identified a number of associations with pancreatic cancer risk and survival. Further studies are needed to determine the specific contribution of these SNPs, genes and signaling pathways to this disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support: National Cancer Institute CA122340 (F.J.C.) and P50CA102701 (G.P.)

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Table 1

Characteristics of pancreatic cancer cases and unaffected controls

Variable	Cases (n=1143)		Controls (n=1097)		p value
	n	%	n	%	
Mean age at diagnosis or recruitment	65.5		65.6		0.79
Age < 60 yrs.	329	(29%)	297	(27%)	0.37
Gender - Male	668	(58%)	557	(51%)	<.001
Ethnicity - Non-Hispanic Whites*	1143	(100%)	1097	(100%)	
Smoking					
Ever-smoker	682	(60%)	505	(46%)	<.001
Smoking status					<.001
Never-smoker**	455	(40%)	592	(54%)	
Former smoker	527	(47%)	458	(42%)	
Current smoker	148	(13%)	41	(4%)	
Missing	13		6		
Years smoked (±SD)	22.4	± 16.9	18.2	± 14.0	<.001
Pack-years smoked (±SD)	17.0	± 23.0	9.3	± 17.2	<.001
Body Mass Index (±+SD)	27.8	± 5.5	27.2	± 4.7	0.01
Region					<.001
MN, IA, or WI (Tristate)	579	(51%)	748	(68%)	
North or South Dakota	94	(8%)	40	(4%)	
Other USA	448	(39%)	308	(28%)	
Other Country	22	(2%)	1	(0%)	
Pancreas Cancer Status at Enrollment					
Resected	328	(29%)	--	--	
Locally advanced	379	(33%)	--	--	
Metastatic	430	(38%)	--	--	
Not specified	6	(1%)	--	--	
Family History of Pancreatic Cancer (1st degree)	79	(7%)	43	(4%)	0.002

*Only Non-Hispanic whites included in the analysis

** Defined as less than 100 cigarettes in lifetime.

Table 2

Genotype-specific risks for pancreatic cancer

Locus	Chr	SNP	OR (95%CI)	Ptrend	Adjusted OR* (95%CI)	Ptrend
DOCK7	1	rs1748197	1.02 (0.9, 1.16)	0.76	1.03 (0.90, 1.17)	0.67
GPSM2	1	rs12090453	1.08 (0.96, 1.22)	0.19	1.07 (0.94, 1.21)	0.31
NEK7	1	rs2884765	0.90 (0.73, 1.10)	0.30	0.91 (0.73, 1.12)	0.36
RRM2	2	rs6759180	0.98 (0.86, 1.12)	0.78	0.99 (0.87, 1.13)	0.85
SMC6L	2	rs6743259	0.99 (0.74, 1.31)	0.93	1.00 (0.75, 1.34)	0.99
RYK	3	rs9283588	0.95 (0.79, 1.14)	0.58	0.95 (0.79, 1.14)	0.58
TOPBP1	3	rs10935070	0.99 (0.87, 1.12)	0.81	0.98 (0.86, 1.11)	0.70
TACC3	4	rs1374468	0.99 (0.86, 1.15)	0.94	0.96 (0.82, 1.11)	0.56
APC	**5**	**rs2431238**	**1.14 (1.01, 1.30)**	**0.035**	**1.14 (1.00, 1.29)**	**0.05**
PLK2	5	rs697141	1.03 (0.90, 1.17)	0.72	1.04 (0.91, 1.19)	0.54
FYN	6	rs1465061	0.91 (0.81, 1.03)	0.13	0.91 (0.80, 1.03)	0.12
RIPK1	6	rs12209182	1.09 (0.97, 1.23)	0.16	1.08 (0.96, 1.22)	0.21
MCPH1	8	rs2433149	1.10 (0.97, 1.25)	0.13	1.09 (0.95, 1.24)	0.22
RAD21	8	rs4579555	1.12 (0.93, 1.35)	0.25	1.10 (0.91, 1.34)	0.33
CDC37	9	rs5022070	1.01 (0.89, 1.14)	0.89	1.02 (0.90, 1.15)	0.78
EIF3S10	10	rs10787899	1.06 (0.94, 1.19)	0.37	1.02 (0.90, 1.15)	0.74
KIAA0999	11	rs7928320	0.96 (0.83, 1.11)	0.55	0.97 (0.84, 1.12)	0.68
SART1	11	rs679581	1.04 (0.93, 1.17)	0.50	1.06 (0.93, 1.20)	0.38
CDC16	13	rs7998576	1.03 (0.90, 1.18)	0.70	1.02 (0.89, 1.18)	0.76
NIN	14	rs9788504	0.93 (0.83, 1.05)	0.25	0.94 (0.83, 1.06)	0.33
NIN	**14**	**rs10145182**	**0.88 (0.78, 0.99)**	**0.038**	**0.89 (0.79, 1.01)**	**0.06**
SNW1	14	rs1477261	0.93 (0.80, 1.09)	0.36	0.95 (0.84, 1.11)	0.54
MAP2K1	15	rs7181936	0.89 (0.79, 1.01)	0.06	0.91 (0.80, 1.03)	0.13
PRC1	15	rs10520699	1.13 (0.95, 1.35)	0.18	1.12 (0.93, 1.34)	0.23
AXIN2	17	rs11079571	0.98 (0.84, 1.15)	0.82	0.95 (0.81, 1.11)	0.51
PRKCA	17	rs7342847	0.90 (0.80, 1.02)	0.09	0.92 (0.81, 1.03)	0.16
TEX14	17	rs302864	0.92 (0.75, 1.13)	0.44	0.88 (0.71, 1.09)	0.23
TLK2	17	rs2245092	0.99 (0.88, 1.13)	0.94	1.01 (0.89, 1.14)	0.91

Locus	Chr	SNP	OR (95%CI)	Ptrend	Adjusted OR* (95%CI)	Ptrend
TUBG1	17	rs2134808	1.02 (0.89, 1.17)	0.76	1.02 (0.88, 1.17)	0.82
YPEL2	17	rs12936897	1.06 (0.95, 1.20)	0.30	1.07 (0.94, 1.21)	0.30
ROCK1	18	rs17202375	1.09 (0.89, 1.34)	0.41	1.06 (0.85, 1.31)	0.60
CABLES2	20	rs8668	1.08 (0.95, 1.23)	0.27	1.08 (0.94, 1.23)	0.28
SUMO3	21	rs2017089	1.01 (0.85, 1.19)	0.95	1.01 (0.85, 1.20)	0.94

*OR and 95%CI after adjustment for age at diagnosis, gender, ever/never smoking, BMI and family history of pancreatic cancer.

Table 3

Genotype specific risks of pancreatic cancer in subgroups based on BMI and smoking

Gene	SNP	Strata	Cases	Controls	OR (95%CI)	Ptrend
TOPBP1	rs10935070	Current smoker	148	41	2.35 (1.26, 4.35)	0.007
		Pack-years <20	186	284	1.35 (1.03, 1.79)	0.03
APC	rs2431238	BMI >=30	374	239	1.31 (1.02, 1.67)	0.031
PLK2	rs697141	Pack-years <20	186	284	1.43 (1.07, 1.92)	0.016
FYN	rs1465061	Pack-years >=40	135	77	0.59 (0.39, 0.91)	0.016
RIPK1	rs12209182	Non-smoker	455	592	1.22 (1.02, 1.44)	0.027
MCPH1	rs2433149	Ever-smoker	682	505	1.20 (1.00, 1.43)	0.044
		Former smoker	527	458	1.22 (1.01, 1.47)	0.044
		BMI <30	769	858	1.17 (1.01, 1.35)	0.042
RAD21	rs4579555	Non-smoker	455	592	1.50 (1.14, 1.96)	0.003
NIN	rs10145182	Ever smoker	682	505	0.82 (0.69, 0.97)	0.01
SNW1	rs1477261	Pack-years <20	186	284	0.61 (0.43, 0.87)	0.006
MAP2K1	rs7181936	BMI <30	769	858	0.86 (0.75, 1.00)	0.049

Gene	SNP	Strata	Cases	Controls	OR (95%CI)	Ptrend
PRC1	rs10520699	BMI >=30	374	239	1.52 (1.05, 2.22)	0.028
PRKCA	rs7342847	Current smoker	148	41	0.53 (0.31, 0.89)	0.017
		BMI >=30	374	239	0.78 (0.61, 0.99)	0.041
TEX14	rs302864	BMI >=30	374	239	0.67 (0.46, 0.98)	0.036
YPEL2	rs12936897	BMI >=30	374	239	1.27 (1.00, 1.62)	0.048

Analyses were adjusted for age at diagnosis, sex, and smoking history (ever, never)

Table 4

Genotype specific associations with pancreatic cancer survival

Cancer status	Gene	SNP	Overall survival HR (95% CI)	P-value
Overall				
	EIF3S10	rs10787899	1.22 (1.05, 1.41)	0.009
Resected				
	GPSM2	rs12090453	0.64 (0.47, 0.88)	0.006
	KIAA0999	rs7928320	0.68 (0.49, 0.95)	0.022
	TUBG1	rs2134808	1.41 (1.04, 1.91)	0.026
	TEX14	rs302864	0.59 (0.38, 0.91)	0.017
	AXIN2	rs11079571	0.61 (0.44, 0.86)	0.005
Locally advanced				
	APC	rs2431238	0.75 (0.59, 0.95)	0.017
	TLK2	rs2245092	1.3 (1.03, 1.65)	0.027

Survival time was based on date of diagnosis to date of death/last contact. Analyses were adjusted for age at diagnosis, sex, and stage of disease (resected, locally advanced, metastatic).