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Mitochondrial genetic polymorphisms do not predict survival in patients with pancreatic cancer

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Abstract

Pancreatic cancer (PC) is a highly lethal malignancy, and the majority of patients succumb to the disease within two years. We evaluated the role of variants of mitochondrial DNA (mtDNA) and mitochondrial haplogroups in predicting prognosis of patients with PC. A total of 24 mitochondrial single nucleotide polymorphisms (mtSNPs) were genotyped in 990 patients with PC. After adjusting for covariates and multiple comparisons, no association between any of the mtSNPs or haplogroups and survival was observed.

Introduction

Pancreatic cancer is expected to affect 37,170 patients in the United States in 2007 and 33,370 will to succumb to the disease.(1) Mutations of mitochondrial DNA (mtDNA) have frequently been observed in human cancers. Recent data suggest that certain mtDNA single nucleotide polymorphisms (mtSNPs) may correlate with poorer prognosis in patients with advanced pancreatic cancer.(2,3) It was reported that a mtSNP in the 16519 mtDNA nucleotide was found to be associated with worse prognosis; a subgroup of patients without distant metastases or vascular invasion appeared to have worse survival in the presence of the 16519T allele when compared to the 16519C allele (3). 16519 mtSNPs have been associated with endometrial cancer(4) and with nonmalignant conditions such as type 2 diabetes mellitus(5) and iron overload disorders.(6). We examined the association of 24 common mitochondrial DNA SNPs (mtSNPs), including 16519 mtDNA, with prognosis in a large cohort of patients with pancreatic cancer.

Materials and Methods

Adult patients with histologically confirmed pancreatic adenocarcinoma seen at Mayo Clinic were identified through an ultra-rapid identification system and invited to participate in a prospective study and registry of pancreatic cancer. Blood samples, clinical information, and risk factor data were collected. The registry performs followup of all patients by chart review,

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mailed surveys, and linkages to the Mayo Tumor Registry and the National Death Index(7). Twenty-four SNPs were selected based on allele frequency, haplogroup and tagSNPs. There were 17 SNPs in the mitochondrial coding region and 7 common SNPs in the regulatory region (D-loop). Genotyping methods using GenomeLab SNPstream system (Beckman Coulter, Inc. Fullerton, CA) were reported in detail previously.(8)

Kaplan-Meier survival analyses (time to event (death) was the time between the diagnosis of pancreatic cancer and death) were implemented to examine the univariate associations between mtSNP allele and survival post-diagnosis of pancreatic cancer. Cox proportional hazards regression models were utilized to test the association after adjusting for covariates (age, gender, smoking history (ever/never), stage at diagnosis, and treatment received (chemotherapy and/or radiation (no/yes)). Analyses were performed on the overall group as well as stratified by whether surgery was performed (no/yes). Hazard ratios and 95% confidence intervals were used to quantify any significant associations. To account for multiple testing, Bonferroni correction was used. Analyses were performed using SAS version 9.1.3.

Results

990 patients with pancreatic cancer seen at Mayo Clinic between October 1, 2000 and February 23, 2006 were included in our analysis (Table 1). The call rates for the genotyping of each of the mtSNPs ranged from 94.2 to 99.6%. Information regarding the patients' vital status through February 6, 2007 was ascertained. Twelve month survival status was available for 913 of the patients (92%). We found no evidence that any of the mtSNPs or haplogroups predicted survival when the entire cohort was evaluated before or after adjusting for covariates (age at diagnosis, sex, stage, smoking status, chemotherapy and radiation therapy).

When patients who did not undergo surgery were analyzed separately, only two mtSNPs showed a trend towards a correlation with survival (16189G, hazard ratio (HR) 1.25, p=0.06 and 1719G, HR 0.70, p=0.07 after adjusting for covariates) (Table 2). No such correlation was found for patients undergoing surgery. The 16519T allele previously reported by other investigators to be associated with prognosis(3), did not predict survival in patients with pancreatic cancer (HR 0.96, p=0.11) when the entire cohort was analyzed or when patients were analyzed according to whether they underwent resection or not. Patients with resectable tumors were, however, less likely to have the 16519T allele when compared to patients not undergoing resection (30% vs. 39%).

When patients surviving less than 6 months were compared to those surviving more than 6 months, an association was found for two alleles. The patients surviving more than 6 months were more likely to have the 709G allele (89% vs. 82%, p =0.022) and the 13368C allele (93% vs. 89%, p=0.027) but after adjusting for multiple comparisons, this difference was not significant.

Discussion

This large study evaluated 24 mitochondrial SNPs in 990 patients with pancreatic cancer and did not show any relationship between the evaluated mtSNPs or haplogroups and survival. While there was a trend toward significance for the 1719G and 16189G alleles, this disappeared after adjusting for multiple comparisons. The 16189 nucleotide was of potential interest because it is located within the highly polymorphic D-loop of the mtDNA. However, using our large sample of patients, we did not observe any difference in survival among patients carrying these mtSNPs, or 16519, even after analyzing patients with resectable cancers separately.

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In conclusion, our findings indicate that the evaluated mtSNPs have no clinically significant value in predicting prognosis in patients with pancreatic cancer.

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Table 1

Patient characteristics

	(N=990)
Age at Pancreas Cancer Diagnosis	65.3 ± 10.7
Gender	
Female	409 (41%)
Male	578 (59%)
Smoking Status	
Never Smoker	363 (37%)
Smoker	607 (63%)
Diabetes Reported	
No	785 (79%)
Yes	203 (21%)
Race	
American Indian/Alaskan	3 (0%)
Asian/Asian-American	5 (1%)
Black/African-American	20 (2%)
White/Caucasian	953 (97%)
Multiracial	1 (0%)
Pancreas Cancer Stage	
Resectable	281 (29%)
Locally Advanced	335 (34%)
Metastatic	368 (37%)
Surgery	
No	655 (66%)
Yes	335 (34%)
Chemotherapy Reported	
No	492 (53%)
Yes	439 (47%)
Radiation Reported	
No	598 (64%)
Yes	333 (36%)

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Table 2

Lack of association of selected mtSNPs with overall survival

Marker	Unadjusted		Adjusted	
	Hazard ratio	95% CI	Hazard ratio	95% CI
All patients				
709G	0.79	0.62 – 1.01	1.02	0.78 – 1.34
1719G	0.91	0.65 – 1.26	0.85	0.60 – 1.19
16189G	1.21	0.99 – 1.47	1.18	0.96 – 1.45
16519T	1.02	0.88 – 1.18	0.96	0.83 – 1.11
Resected				
709G	1.05	0.59 – 1.86	1.08	0.60 – 1.94
1719G	1.21	0.62 – 2.35	1.30	0.63 – 2.67
16189G	0.94	0.61 – 1.43	1.09	0.71 – 1.67
16519T	1.14	0.87 – 1.51	1.08	0.81 – 1.45
Not resected				
709G	0.78	0.59 – 1.03	0.96	0.70 – 1.31
1719G	0.68	0.47 – 1.00	0.70	0.48 – 1.03
16189G	1.36	1.09 – 1.70	1.25	0.99 – 1.60
16519T	0.90	0.77 – 1.07	0.91	0.76 – 1.08