RESEARCH ARTICLE

Association of the CYP17-34T/C Polymorphism with Pancreatic Cancer Risk

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Abstract

Pancreatic cancer is a leading cause of fatality worldwide. Several population studies have been conducted on genetic diagnosis of pancreatic cancer but the results from epidemiologic studies are very limited. CYP17A gene has a role in disease formation but its influence on pancreatic cancer is unclear. A polymorphism in the 5'UTR promoter region of CYP17A1-34T/C (A1/A2) has been associated with multiple cancers. The aim of the current study was to assess associations of this polymorphism and socio-demographic risk factors with pancreatic cancer. A total of 255 and 320 controls were enrolled in the study, and were genetically analyzed through PCR-RFLP. Statistical analysis was conducted with observed genotype frequencies and odds ratios (ORs) and 95% CIs were estimated using unconditional logistic regression. The impact of socio-demographic factors was accessed through Kaplen-Meir analysis. According to our results, the A2/A2 genotype was significantly associated with pancreatic cancer (OR=2.1, 95%CI = 1.3–3.5). Gender female (OR=2.6, 95%CI=1.8–3.7), age group 80s/80+ years (OR=2.2, 95% CI=1.2-4), smoking both former (OR=4.6, 95% CIs=2.5-8.8) and current (OR=3.6, 95% CI=2-6.7), and family history (OR=7.1; 95%CI = 4.6-11.4) were also found associated with increased risk. Current study suggests that along with established risk factors for pancreatic cancer CYP17A1-34T/C may play a role. However, on the basis of small sample size the argument cannot be fully endorsed and larger scale studies are recommended.

Keywords: CYP17A1 A1/A2 polymorphism - pancreatic cancer - PCR-RFLP - statistical analysis

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Introduction

Pancreatic cancer is a common type of carcinoma in Western countries indicating the fourth most common in male and the 5th most common in females. The death rate of pancreatic cancer has a medium survival of 6 months. (Klopel at al., 2000). The older age, male gender and black people are found to be mostly affected. Certain studies have shown association of fatty diet, pesticides and smoking with pancreatic cancer. Its association is also observed with type 2 diabetes mellitus and is up to 10% familial (kemery, 2006). The pathological varieties described include, islet cell carcinomas (5%), cyst adenocarcinoma and ductal cell adenocarcinoma (90%) (Capelle at al., 2000).

The diagnosis of pancreatic cancer is confirmed histologicaly as well: other associated symptoms like anorexia, weight loss and epigastric pain leading to spread to other sites like peritoneum causing ascites, regional nodes, the lungs, and liver (Steer, 2005). Currently the treatment is not much effective (Laethem and Marechal, 2007). Pancreatic resection duodenectomy, and chemotherapy are thought as the best option but it is so if the tumor size is less than 3 cm (Fernandez-del at al., 2005).

As smoking is the most commonly associated factor with cancer, so in the case of pancreatic cancer, this factor is also found prominent in several studies. Current smokers category has shown 1.7-fold increased risk (95% CI=1.6–19), while former smokers are less susceptible with 1.2-fold (95% CI=1.1–1.3) (Iodice at al., 2008). Similarly, type 2 diabetes is also among the factors with the increased risk, odds ratio (OR)=1.8 (95% CI=1.5–2.1) compared with non-diabetics. Risk of pancreatic cancer is also found increasing with the increase of BMI OR=1.6 (95% CI=1.2–2.1) for individuals with BMI >35 compared to individuals with BMI of 18.9–24.9 (Arslan et al., 2010). Heavy alcohol consumers are at pancreatic cancer risk OR=1.46 (95% CI=1.2–1.8) compared with non alcoholic individuals (Lucenteforte at al., 2011).

Like other cancers, pancreatic cancer also is basically a genetic disorder caused both by inherited and acquired genetic factors. Inherited genetic alterations contribute majorly towards both the familial and non-familial types of pancreatic cancer. Approximately 5–10% of the cases have a family history of pancreatic cancer (Hurban at al., 2010; Lynch at al., 1996). Several genes responsible for pancreatic cancer have already been

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established including both high-penetrance (Murphy at al., 2002; Su at al., 1999; Lynch at al., 2002) and low penetrance genes (Amundadottir at al., 2009).

A1A2 (-34T/C) polymorphism located in the 5′UTR is one of the most studied SNP in CYP17A1 (Sharp at al., 2004) which has already been studied in breast cancer, prostate cancer etc. With the same aim we also made an attempt to investigate the association of CYP17A1 gene with increased risk of pancreatic cancer in Pakistani population.

Materials and Methods

Samples for case-control study of pancreatic cancer were majorly collected from NORI hospital, Islamabad, Pakistan. This study was approved by the Departmental scientific committee of Capital University of Science and Technology, Islamabad and was based upon 255 cases and 320 controls. A performa was designed for information collection. Participants were directly convinced and samples along with required clinical parameters were collected along with informed signed consent. The clinical parameters included in our study were age, family history of cancer, sex and smoking. No proxy interviews were considered. Age was divided into six groups (below 40, 40s, 50s, 60s, 70s and 80s/80+ years of age groups). Samples were collected from the four provinces including Punjab, Khyber Pakhtunkhwa (KPK), Sindh, Baluchistan and Kashmir. Smokers were divided into three main groups as current smoker, former smokers and never smoked category. Family history was also termed as mandatory to be reported in the questionnaire. In gender, only two sexes (Male and Female) were found only with no unknown category. After DNA extraction the gene A 459bp fragment of CYP17A1 gene containing the 5'UTR was amplified by using the forward primer 5'-CATTCGCACCTCTGGAGTC-3' and reverse primer 5'-GGCTCTTGGGGTACTTG-3' as described by Feigelson et al. (1997). The A1A2 SNP was genotyped by using restriction endonuclease MspAI.

Statistical analysis was conducted with observed genotype frequencies (A1A1, A1A2 and A2A2 Alleles). Odds ratios (ORs) and 95% CIs were estimated by using unconditional logistic regression. The impact of socio-demographic factors was accessed through Kaplen-Meir analysis. All models were adjusted for age, family history, smoking and sex. All analysis was conducted using R 3.1.

Results

Overall, patients were from different regions of Pakistan

Table 1. Socio-Demographic Characteristics of Cases-Control Study Population

	cases					Controls				
Factors	No	%age	Mean	SD	Range	No	%age	Mean	SD	Range
Age	255		66.8	11.1	29.0-91.0	320.0		61.8	9.6	34.0-81.0
Age groups										
Below 40	2.0	0.8	32.0	3.5	29.0-35.0	6.0	1.9	36.7	1.9	34.0-39.0
40s	14.0	5.5	46.5	2.6	41.0-49.0	27.0	8.4	45.0	2.6	40.0-49.0
50s	48.0	18.8	54.8	3.1	50.0-59.0	91.0	28.4	55.0	2.8	50.0-59.0
60s	91.0	35.7	65.1	2.2	60.0-69.0	118.0	36.9	64.5	2.8	60.0-69.0
70s	67.0	26.3	74.5	2.7	70.0-79.0	58.0	18.1	73.2	2.3	70.0-78.0
80s/80+	33.0	12.9	83.0	3.3	80.0-91.0	20.0	6.2	82.6	0.5	80.0-86.0
Family history										
Yes	28.0	11.0				106.0	33.1			
No	148.0	58.0				291.0	90.9			
Sex										
Male	160.0	62.7				245.0	76.6			
Female	113.0	44.3				75.0	23.4			
Geographical distribution										
Punjab	140.0	54.9								
KPK	97.0	38.0								
Sindh	8.0	3.1								
Balochistan	6.0	2.3								
Kashmir	4.0	1.6								
Smoking										
Current smoker	16.0	6.3				66.0	20.6			
Former smoker	80.0	31.4				72.0	22.5			
Never smoked	159.0	62.3				182.0	56.9			

Table 2. Association between CYP17 (A1/A2) Polymorphism and Pancreatic Cancer

	Cases (255)	Controls (320)	OR(95% CI)	Z value	P value
A1 allele	266.0	392.0			
A2 allele	244.0	248.0			
Allelic contrast	244.0	248.0	1.4(1.1-1.8)	3.1	0.0
A1A1	72.0	119.0	Ref		
A1A2	122.0	154.0	1.3(0.9-1.9)	1.4	0.2
A2A2	61.0	47.0	2.1(1.3-3.5)	3.1	0.0
Dominant	183.0	201.0	1.5(1.1-2.1)	2.3	0.0
Recessive	61.0	47.0	1.3(0.9-2.1)	1.3	0.2

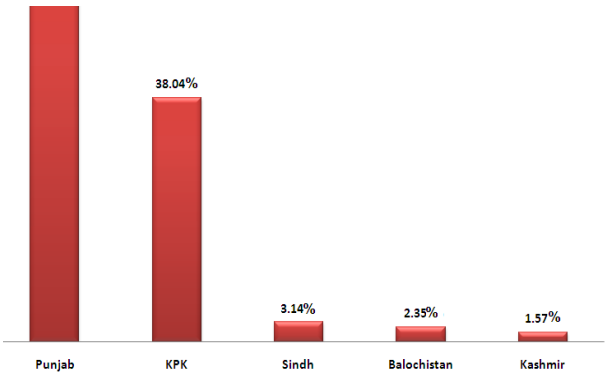

Figure 1. Distribution of Cases in Pakistan of the Basis of the Geographical Background

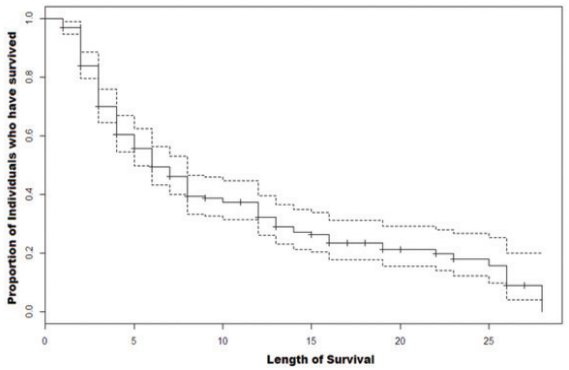

Figure 2 . Plot of Overall Survival Curve for Pancreatic Cancer Patients

Table 3. Uni-Factorial Analysis and Distribution of Socio-Demographic Factors

Age groups	Cases (255)	Controls (320)	OR(95%CI)	Z	P
below 40	2.0	6.0	0.4(0.1-2.1)	-1.1	0.3
40s	14.0	27.0	1.0		
50s	48.0	91.0	0.6(0.4-0.9)	-2.7	0.0
60s	91.0	118.0	0.9(0.7-1.3)	-0.3	0.8
70s	67.0	58.0	1.6(1.1-2.4)	2.3	0.0
80s/80+	33.0	20.0	2.2(1.2-4)	2.70	0.0
Family history					
Yes	28.0	106.0	7.1(4.6-11.4)	8.4	0.0
No	148.0	291.0	1.0		
Sex					
Male	160.0	245.0	1.0		
Female	113.0	75.0	2.6(1.8-3.7)	5.2	0.0
Smoking					
Current smoker	16.0	66.0	3.6(2-6.7)	4.3	0.0
Former smoker	80.0	72.0	4.6(2.5-8.8)	4.7	0.0
Never smoked	159.0	182.0	1.0		

with the numbers given in Figure 1, (Punjab= 59.9%, KPK= 38%, Sindh= 3.1%, Baluchistan= 2.3%) and Kashmir region (1.6 %).The CYP17A1 polymorphism was found associated with pancreatic cancer in all 255 cases and 320 controls (adjusted for age, sex, race, and smoking status) (Table 2). In genotype results, the CYP17A1 -34 T/C polymorphism satisfied a significant association by observing p value as 0.00 in A2A2 Alleles and the rest of the allelic contrast was found with the p value >0.1 verified by the Odd Ratios and 95% Confidence interval. [A2A2 OR=2.1, 95%CI = 1.3–3.5, followed by Dominant contrast OR=1.5, 95% CI 1.06-2.1; allelic contrast with OR =1.4, 95% CI=1.2-1.8; Resistive OR=1.3, 95% CI=0.9-2.1 and A1A2 with the OR=1.3, 95% CI=0.9-1.9].

The socio-demographic factors were also analyzed for association in which Gender female (OR=2.6,

95%CI=1.8–3.7), age group 80s/80+ Years (OR=2.2, 95% CI=1.2-4), smoking both former (OR=4.6, 95% CIs=2.5-8.8) and current (OR=3.6, 95% CI=2-6.7) and family history (OR=7.1; 95%CI = 4.6-11.4) were found associated with increased risk. Overall survival analysis highlighted that 168 were uncensored among which the median survival time was 6 months (95% CI=5-8) as shown in Figure 2.

The current study was aimed to analyze the CYP17A1 50UTR -34 T/C (A1/A2) polymorphism and some socio-demographic factors (Smoking, Age, Sex and Race) associated with pancreatic cancer, which showed the A2A2 allele polymorphism mostly associated and the socio-demographic factors were also analyzed for association in which Gender female, age group 80s/80+ years, smoking both former and current and with family history of cancer were found associated with increased risk. Overall, survival analysis highlighted that 168 were uncensored among which the median survival time was 6 months.

Discussion

In conclusion, the current study also suggests that some of the established risk factors for pancreatic cancer may also be associated with CYP17A1-34T/C alteration. However, on the basis of small sample size the argument cannot be fully endorsed and large scale studies are recommended. Our study consisted of 255 cases which is a modest figure, so we expect that sample number may affect results. But, apart from this, our study also has a number of strong points like its prospective design to avoid biasness and its case-control nature.

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