

Evaluation of risk factors associated with pancreatic adenocarcinoma in Black Sea region, Turkey

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ABSTRACT

Aim: To evaluate the risk factors in patients with pancreatic adenocarcinoma in Turkey's Black Sea region and to determine groups at high risk for pancreatic cancer.

Methods: 106 newly diagnosed pancreatic adenocarcinoma patients living in Black Sea region of Turkey who applied to our clinic between January 2015 and December 2016 were included in this study. In the same period a control group was formed with 92 patients of similar age. Both groups were asked to fill out a form that questioned the pancreatic cancer risk factors. Data were analyzed.

Results: Pancreatic cancer risk was 3.5 times higher in people over 65 years of age. Patients with deficient level of serum vitamin D level (<20 ng/ml) had 10.2 times more risk of pancreatic cancer than patients with normal level of Vitamin D (≥30 ng/ml). While newly diagnosed type 2 diabetics had 19.5 times higher risk of pancreatic cancer, long term type 2 diabetics had 1.2 times higher risk than normal individuals. Those with pancreatic cancer in family had 4.3 times higher risk than those who did not. It was observed that people with rhesus (Rh) antigen negative blood group has 70% less risk of pancreatic cancer.

Conclusion: Determination of pancreatic cancer risk factors, organization of imaging and screening programs for high-risk people can provide early diagnosis of the disease and prolong survival.

Keywords: Pancreatic adenocarcinoma, risk factors, pancreatic neoplasms, etiology, epidemiology.

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Introduction

Although pancreatic cancer is the 11th most common cancer type, it ranks as the third leading cause of cancer-related death in the USA [2]. Pancreatic cancer is predicted to be the second most common cause of cancer-related deaths in coming 20 years [3]. In a study conducted by Parkin et al. in 2002, pancreatic cancer accounts for 3% of all cancer types

worldwide, however, it is among the top in cancer-related deaths due to its poor diagnosis [1]. In many patients, when pancreatic cancer is detected, the disease is advanced and the tumor is not operable. Median survival rate is less than a year, and mortality rate is approximately 99%. Only less than 10% of pancreatic tumors can be detected at an early phase and resected. Usually the disease starts to develop two years before its diagnosis [4]. Most patients initially have a non-specific pain in epigastrium. As the disease develops in time, the pain spreads over to the back, upper thoracic and lumbar region. Upon progress of the disease, most patients consult doctors with complaints of pain, jaundice, and

loss of weight. It is often the case that when patient seeks medical advice with these complaints, the disease has already reached the advanced stage [1-5].

There are numerous studies conducted to identify causes of pancreatic cancer. In etiology, environmental and genetic causes are considered to play a joint role. Risk factors are divided in two as changeable and unchangeable risk factors. Unchangeable risk factors are age, gender, race, genetic factors, family history, atopy/allergy history, blood groups, surgery history, diabetes and chronic pancreatitis. Changeable risk factors, on the other hand, can be listed as smoking, obesity, use of alcohol, dietary, socio-economic conditions, infections, levels of vitamin D and folic acid. Analysis of risk factors and identification of factors that significantly increases the risk are of high importance [1-10]. Identifying populations of high-risk, establishing imaging and screening programs for these groups can support early diagnosis of the disease and increase survival period. Therefore, in this study, we aimed to identify high-risk groups together with risk factors in patients with pancreatic adenocarcinoma in Turkey's Black Sea region.

Materials and Methods

Ethical approval for this study was obtained from the local ethics committee (IRB approval number 144/2015). Necessary permissions were obtained from the hospital and families. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

106 newly diagnosed pancreatic adenocarcinoma patients living in Black Sea Region of Turkey who applied to our clinic

between January 2015 and December 2016 were included in this study. In the same period, a control group was also formed with 92 patients of similar age group who visited our clinic for another disease and had not been diagnosed with cancer. Both groups were asked to fill out a form that questioned the risk factors. The factors to be investigated in this study, conducted as a case-controlled and cross-sectional study, are defined as follows: age (≤ 50 , 51-65, > 65); gender (female, male); family history of pancreatic cancer (yes, no); atopy/allergy (yes, no); blood type (A,B,O,AB; rhesus (Rh) antigen negative, Rh antigen positive); cholecystectomy (yes, no); gastrectomy (yes, no); type 2 diabetes (yes, no); duration of diabetes - newly diagnosed type 2 diabetes (< 2 years), long term type 2 diabetes (≥ 2 years); smoking (never smoked, still smoking or stopped smoking); body mass index (BMI) normal weight (18.5-24.99), pre-obesity (25-29.99), obesity (≥ 30); alcohol consumption (yes, no); place of residence (rural, urban); helicobacter pylori history (yes, no); level of vitamin D normal (> 30 , 80 ng/ml), insufficient (20, ≤ 30 ng/ml), deficient (< 20 ng/ml); level of folic acid low (< 4.6 ng/ml), normal (4.6-18.7 ng/ml), high (> 18.7 ng/ml).

Statistical analysis

The collected data were analyzed with IBM SPSS V23. In the evaluation of the study data, besides the descriptive statistical methods (mean, standard deviation), in the comparison of qualitative data; Pearson's chi-squared test were used. The p-value < 0.05 was significantly considered. Independent Sample T-test was applied in the analysis of the significance of the difference between the averages obtained.

Results

There was no significant difference across groups concerning age and gender ($p > 0.05$)

(see Table 1). Pancreatic cancer risk was found 3.5 times higher in patients over 65 years of age compared to the control group ($p < 0.05$). Gender was not associated with increased pancreatic cancer risk ($p > 0.05$). The risk of pancreatic cancer was observed 3.4 times higher in people with insufficient serum vitamin D level. For people with deficient level of serum vitamin D, the risk increased 10.2 times more ($p < 0.05$). When non-smokers were taken as reference, there was no increase in the risk of pancreatic cancer in individuals who quit smoking or who are smoking ($p > 0.05$). The risk of pancreatic cancer was detected to increase 1.2-fold in diabetic patients ($p < 0.05$). When diabetic patients were classified as newly diagnosed type 2 diabetes (< 2 years) and long-term type 2 diabetes (≥ 2 years), the risk of pancreatic cancer increased by 19.5-fold in newly diagnosed type 2 diabetic patients ($p < 0.05$). There was no association between BMI, alcohol use, chronic pancreatitis and pancreatic cancer risk ($p > 0.05$). Compared to the control group, the risk of pancreatic cancer was observed to increase 4.3-fold in patients with pancreatic cancer history in the family ($p < 0.05$).

There was no significant difference in terms of pancreatic cancer risk between those living in urban areas and rural areas ($p > 0.05$). Similarly, we observed no relation between the level of serum folic acid, distribution of ABO blood types, helicobacter pylori, atopy/allergy, gastrectomy, cholecystectomy, and the risk of pancreatic cancer ($p > 0.05$). However, the risk of pancreatic cancer was found less patients with Rh antigen negative blood group ($p < 0.05$) (See table 2).

There was no significant difference across groups concerning age and gender ($p > 0.05$) (See Table 1). Pancreatic cancer risk was found 3.5 times higher in patients over 65 years of age compared to the control group ($p < 0.05$). Gender was not associated with increased pancreatic cancer risk ($p > 0.05$). The risk of pancreatic cancer was observed 3.4 times higher in people with insufficient serum vitamin D level. For people with deficient level of serum vitamin D, the risk increased 10.2 times more ($p < 0.05$). When non-smokers were taken as reference, there was no increase in the risk of pancreatic cancer in individuals who quit smoking or who are smoking ($p > 0.05$). The risk of pancreatic cancer was detected to increase

Table 1. Age and gender distribution.

Parameters	Pancreatic Cancer	Control Group	<i>P value</i>
Average age (Years)	65 $\pm$ 11	62 $\pm$ 13	0.207
Age groups ≤ 50	11 (10.4%)	19 (20.7%)	0.052
51-65	33 (31.1%)	33 (35.9%)	
>65	62 (58.5%)	40 (43.5%)	
Gender Male	63 (59.4%)	52 (56.5%)	0.679
Female	43 (40.6%)	40 (43.5%)	

Table 2. Comparison of pancreatic cancer risk factors between groups.

Parameters	Pancreatic Cancer Group	Control Group	OR	P
Age groups				
≤50	11 (10.4%)	19 (20.7%)	Reference	0.014
51-65	33 (31.1%)	33 (35.9%)	1.3 (0.4 – 4.1)	
>65	62 (58.5%)	40 (43.5%)	3.5 (1.2 – 10.2)	
Gender				
Male	63 (59.4%)	52 (56.5%)	Reference	0.616
Female	43 (40.6%)	40 (43.5%)	0.9 (0.4 – 2.2)	
Serum vitamin D level (ng/ml)				
Normal (>30, 80)	3 (2.8%)	10 (10.9%)	Reference	0.001
Insufficient (20, ≤30)	6 (5.7%)	15 (16.3%)	3.4 (0.5 – 25.4)	
Deficient (<20)	97 (91.5%)	67 (72.8%)	10.2 (2 – 52.6)	
Smoking				
Never smoked	51 (48.1%)	52 (56.5%)	Reference	0.242
Still smoking or smoked before/quit smoking	55 (51.9%)	40 (43.5%)	1.6 (0.7 – 3.8)	
Body mass index (kg/m²)				
Normal (18.5-24.99)	22 (20.8%)	28 (30.4%)	Reference	0.757
Pre-obesity (25-29.99)	44 (41.5%)	32 (34.8%)	1.7 (0.7 – 4.3)	
Obesity (≥30)	40 (37.7%)	32 (34.8%)	1.3 (0.5 – 3.6)	
Type 2 diabetes				
No	65 (61.3%)	73 (79.3%)	Reference	0.001
Yes	41 (38.7%)	19 (20.7%)	1.2 (0.4 – 3.1)	
Duration of type 2 diabetes (years)				
No	65 (61.3%)	73 (79.3%)	Reference	0.003
Newly diagnosed type 2 diabetes (<2 years)	23 (21.7%)	2 (2.2%)	19.5(3 – 127.3)	
Long term type 2 diabetes (≥2 years)	18 (17.0%)	17 (18.5%)	1.2 (0.6 – 2.5)	
Family history of pancreatic cancer				
No	96 (90.6%)	89 (96.7%)	Reference	0.041
Yes	10 (9.4%)	3 (3.3%)	4.3 (0.8 – 22.3)	
Alcohol consumption				
No	88 (83.0%)	77 (83.7%)	Reference	0.796
Yes	18 (17.0%)	15 (16.3%)	0.9 (0.3 – 2.6)	
Place of residence				
Rural	50 (47.2%)	27 (29.3%)	2 (0.9 – 4.3)	0.054
Urban	56 (52.8%)	65 (70.7%)	Reference	
Chronic pancreatitis history				
No	104 (98.1%)	91 (98.9%)	Reference	0.814
Yes	2 (1.9%)	1 (1.1%)	0.7 (0.1 – 32.4)	
Helicobacter pylori history				
No	93 (87.7%)	85 (92.4%)	Reference	0.310
Yes	13 (12.3%)	7 (7.6%)	1.5 (0.5 – 5.3)	
Serum folic acid level (ng/ml)				
Low (0, <4.6)	9 (8.5%)	18 (19.6%)	Reference	0.099
Normal (4.6-18.7)	91 (85.8%)	69 (75.0%)	3.7 (1.2 – 11.5)	
High (>18.7)	6 (5.7%)	5 (5.4%)	2.8 (0.5 – 15.1)	
Blood groups				
O	30 (28.3%)	32 (34.8%)	Reference	0.835
A	56 (52.8%)	36 (39.1%)	1.5 (0.7 – 3.4)	
B	14 (13.2%)	19 (20.7%)	0.6 (0.2 – 1.8)	
AB	6 (5.7%)	5 (5.4%)	1.1 (0.2 – 5.4)	
Rh status				
Rh antigen negative	91 (85.8%)	69 (75.0%)	Reference	0.006
Rh antigen positive	15 (14.2%)	23 (25.0%)	0.3 (0.1 – 0.8)	
Atopy/allergy				
No	99 (93.4%)	82 (89.1%)	Reference	0.453
Yes	7 (6.6%)	10 (10.9%)	0.6 (0.1 – 2.3)	
Cholecystectomy				
No	91 (85.8%)	83 (90.2%)	Reference	0.466
Yes	15 (14.2%)	9 (9.8%)	1.6 (0.5 – 5.3)	
Gastrectomy				
No	102 (96.2%)	90 (97.8%)	Reference	0.926
Yes	4 (3.8%)	2 (2.2%)	1.1 (0.2 – 8.2)	

1.2-fold in diabetic patients ($p < 0.05$). When diabetic patients were classified as newly diagnosed type 2 diabetes (< 2 years) and long-term type 2 diabetes (≥ 2 years), the risk of pancreatic cancer increased by 19.5-fold in newly diagnosed type 2 diabetic patients ($p < 0.05$). There was no association between BMI, alcohol use, chronic pancreatitis and pancreatic cancer risk ($p > 0.05$). Compared to the control group, the risk of pancreatic cancer was observed to increase 4.3-fold in patients with pancreatic cancer history in the family ($p < 0.05$). There was no significant difference in terms of pancreatic cancer risk between those living in urban areas and rural areas ($p > 0.05$). Similarly, we observed no relation between the level of serum folic acid, distribution of ABO blood types, helicobacter pylori, atopy/allergy, gastrectomy, cholecystectomy, and the risk of pancreatic cancer ($p > 0.05$). However, the risk of pancreatic cancer was found less patients with Rh antigen negative blood group ($p < 0.05$) (see Table 2).

Discussion

In the United States, 10% of pancreatic cancers are under the age of 50. It has been reported that the risk of cancer increases with age [5-7]. When people aged 50 and below are referenced, the risk of pancreatic cancer has increased 3.5-fold for those who are older than 65 ($p < 0.05$). Many studies on pancreatic cancer have not revealed a significant difference between genders [8, 9]. In our study, gender was not correlated to pancreatic cancer risk ($p > 0.05$). The best indicator of vitamin D level in serum is 25-hydroxyvitamin D3. This level is determined by dietary vitamin D and sun exposure. It is stated that serum vitamin D level may vary depending on age, race, BMI and diseases. Experimental studies suggest that the risk of pancreatic cancer may be reduced if the

optimal level of serum vitamin D is achieved, depending on the diet or sun rays. However, clinical studies are inadequate; there are some conflicting data available, too. In one of these, it has been suggested that there may be an increased risk of pancreatic cancer with increased serum 25-hydroxyvitamin D3 levels. However, at the end of the study, the difference was considered to stem from the difference in patient-control group analysis of the studied population or the difference in the method used to measure the level of 25-hydroxyvitamin D3 [10]. In an experimental study conducted by Kasiappan et al. [11] a group of mice with tumors were given a high-fat diet for 30 days; another group with a tumor was given a high-fat diet and the vitamin D analogue seocalcitol (EB1089). When the two groups were compared, tumor growth was more than 50% in mice that did not receive the vitamin D analogue seocalcitol. In our study, the risk of pancreatic cancer increased by 10.2-fold in people with deficient serum D level compared to individuals with normal vitamin D level ($p < 0.05$). Pre-clinical studies contain data which indicates that cancer risk will decrease with vitamin D support. Clinical studies cannot adequately express this. This relationship is maybe really weak; perhaps it may be present in certain cancers.

Smoking is the most important known risk factor associated with pancreatic cancer. In a study, the risk of pancreatic cancer was found to be two times higher in smokers than in nonsmokers. It was stated that this risk would increase in direct proportion with the amount of cigarettes used and the duration of time smoked [12]. According to our data, there was no correlation between smoking and the risk of pancreatic cancer ($p > 0.05$). Based on American Cancer Society studies, those with BMI ≥ 30 had a 2.08 times greater risk of pancreatic

cancer than those with BMI < 25 [13]. In the data obtained, there was no correlation BMI and pancreatic cancer risk ($p>0.05$). Diabetes is a risk factor for pancreatic cancer; it can also be a sign of the emergence of pancreatic cancer or a condition that may occur after surgery. In a meta-analysis of 20 studies conducted by Everhart and Wright in 1995, the risk of pancreatic cancer in diabetic individuals was found to be 2 times more than in non-diabetic [1]. In the data obtained, the risk of pancreatic cancer in diabetic patients was found 1.2 times higher than in non-diabetic patients ($p<0.05$). In a study conducted with 1428 pancreatic cancer and 1528 healthy control groups, the rate of diabetes was 27.6% in people with pancreatic cancer, while the rate of diabetes was 9.9% in people in the control group. Of the patients who have both pancreatic cancer and diabetes, 76.2% had newly diagnosed diabetes, which was significantly higher than the control group [14]. When non-diabetic patients were referenced, the risk of pancreatic cancer increased 19.5-fold in the presence of newly diagnosed type 2 diabetes (<2 years); those with long-term type 2 diabetes (≥ 2 years) had a 1.2-fold increased risk of pancreatic cancer ($p<0.05$).

Familial pancreatic cancer accounts for 10% of all patients with pancreatic cancer. In a study, the risk of pancreatic cancer for people in whose immediate family (mother, father, and siblings) there are at least two with pancreatic cancer increases the risk ten times compared those with no family history [15]. According to our data, the risk of cancer increased 4.3 times in patients with a family history of pancreatic cancer ($p<0.05$). 1530 pancreatic cancer patients and 1530 healthy individuals from the Pancreatic Cancer Cohort Consortium were evaluated in a case-control study. There was no significant statistical difference between those

who had >0 or <5 grams of alcohol daily and those who had ≥ 60 grams of alcohol daily [16]. In another study, it was reported that consuming 40 grams of alcohol daily increased the risk of pancreatic cancer 1.45 times, and that it could increase up to 1.62 times [17]. The results from these studies are contradictory. In our study, there was no correlation between alcohol use and the risk of pancreatic cancer ($p>0.05$).

Research has shown that pancreatic cancer is more common in people living in urban areas with low socioeconomic condition. According to our data, no relationship was found between the place of residence and the risk of pancreatic cancer ($p>0.05$). Four percent of patients with chronic pancreatitis are believed to develop pancreatic cancer [18]. If a person has a history of familial pancreatitis, the risk increases 50-60 times [19]. In our study, there was no correlation between the risk of chronic pancreatitis and pancreatic cancer ($p>0.05$). The International Agency for Research on Cancer classifies the helicobacter pylori as a proven carcinogen. In four contemporary studies conducted, it was iterated that there is a possible relationship between pancreatic cancer and helicobacter pylori, however further studies are needed [20]. According to our data, there was no correlation between helicobacter pylori and pancreatic cancer risk ($p>0.05$). The International Agency for Research on Cancer has proposed that foods containing folate may be protective against pancreatic cancer [21]. In a study evaluating 14 prospective cohort studies that involves 319716 men and 542948 women, the relationship between folate use and pancreatic cancer was investigated. Over 7-20 years after the study, 2195 pancreatic cancers were identified. There was no correlation between folate intake and pancreatic cancer risk when the 15% quartile of the highest folate intake diet and 15% quartile of the lowest folate

intake diet were compared [22]. In the current literature, inconsistent findings have been observed between the amount of folate in the diet and the level of serum folate and the risk of pancreatic cancer. In the data obtained, no correlation between folic acid level and pancreatic cancer risk ($p>0.05$) was found.

In a study conducted on blood types with 224 patients who have pancreatic cancer, the risk was 1.5 times higher in individuals with blood type B than in individuals with other blood types; the risk was lower in individuals with 0 type blood [23]. In our study, there was no correlation between ABO blood types and pancreatic cancer risk ($p>0.05$). It has been investigated whether there is any difference in pancreatic cancer risk based on Rh status or not. According to the statistical analysis, the risk of pancreatic cancer in Rh antigen negative people was 70% less ($p<0.05$). Given the differences in distribution of ABO and Rh blood types of people living all over the world and current studies concerning blood types, further studies are needed to determine whether there is a link between blood types and pancreatic cancer risk. When 13 community-based studies were examined, the risk of pancreatic cancer in atopic/allergic individuals was 30% less [24]. Studies examining the relationship between pancreatic cancer and atopy/allergy suggest that there is need for further studies. According to our data, there was no significant association between atopy/allergy and pancreatic cancer risk ($p>0.05$). A study shows that cholecystectomy increased the risk of pancreatic cancer by 23% and gastrectomy by 50% [25, 26]. In our study, there was no relation between the risk of pancreatic cancer and cholecystectomy and/or gastrectomy ($p>0.05$). In the current literature, the relationship between cholecystectomy or gastrectomy and the risk of pancreatic cancer is not clear enough.

The limitation of this study is that it is case-controlled and cross-sectional. Therefore, the results may suggest that vitamin D deficiency is more common in patients with pancreatic cancer, but we cannot clearly predict the increased risk of pancreatic cancer in cases of vitamin D deficiency. Smoking is a proven risk factor for pancreatic cancer, but this was not demonstrated in our study. On the other hand, a similar situation applies to the relationship between Rh status and pancreatic cancer risk. We cannot expressly conclude that the risk of pancreatic cancer is reduced in people with Rh antigen negative. A population-based follow-up study is required for more reliable results. This article may contribute to the following population-based studies.

The main problem with pancreatic cancer is that the disease cannot be detected early; when diagnosed, the disease is often at an advanced stage. Because the survival rate is low and that diagnosis cannot be made in the early stages of pancreatic cancer, primary prevention is important. Therefore, identification of risk factors and better elucidation of etiology is necessary.

Conclusion

Determination of pancreatic cancer risk factors, organization of imaging and screening programs for high-risk people can provide early diagnosis of the disease and prolong survival. Population-based studies are needed to reveal pancreatic cancer risk factors.

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