Occurrence of Pancreatic Cancer Associated Insulin Dependent Diabetes

Tomislav Denis, Danijel P, Sunčana NK *
Departments of Breast Surgical Oncology, Croatia.
*Corresponding Author: Sunčana NK, Departments of Breast Surgical Oncology, Croatia. Email: suncana@yahoo.com

Received date: June 30, 2017; Accepted date: August 20, 2017; Published date: September 08, 2017.
Citation for this Article: Tomislav Denis, Danijel P, Sunčana NK, Occurrence of Pancreatic Cancer Associated Insulin Dependent Diabetes, J Cancer Research and Cellular Therapeutics, Doi: 10.31579/2640-1053/016

Copyright: © 2017 Sunčana NK. This is an open-access article distributed under the terms of The Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract
Patients with pancreatic cancer often present with non-specific symptoms and are often diagnosed at an advanced stage. The relationship between diabetes and the development of pancreatic cancer has been an area of intense research. In the present study we specifically aim to look at the hypothesis that the incidence of insulin dependent diabetes increases after the onset of pancreatic cancer.

Materials and Methods
We retrospectively reviewed the chart of all pancreatic cancer patients in tumor registry admitted to University of Florida Tumor Registry in Jacksonville, Florida. Data was collective from January 2000 and December 2006. Each patient’s record was reviewed for histologic biopsy, demographic information, presence of risk factors, co-morbidities, presence and duration of diabetes. Assessment of diabetes was based on the guidelines provided by American Diabetes Association.

Results
82 patients were identified from the University of Florida Cancer Registry from the year 2000-2006. Complete data was available on 76 patients. Mean age at diagnosis was 66.4 years. 53 (69.7%) were African American, 23 (30.26%) were white. There was an equal male/female distribution of 1:1.07 (43 males; 40 females). 35 (46.0%) patients were smokers. Most common presentation was with obstructive jaundice (33/76 or 43.4%) followed by typical symptoms of weight loss, fatigue, abdominal and back pain (31/76 or 40.78%). In 11 (14.47%) patients, pancreatic cancer was noted as an incidental finding. Staging at the time of diagnosis was available in 76 patients. 48 (63.1%) patients were in stage 3 and 28 (36.9%) in stage 4. 13 (17.1%) patients were alive at 1 year, 10 (13.5%) patients were alive at 2 years and 5 (6.5%) patients were alive at 5 years. In 11 (14.47%) patients, pancreatic cancer was noted as an incidental finding. Staging at the time of diagnosis was available in 76 patients. 48 (63.1%) patients were in stage 4, 13 (17.1%) patients were in stage 3, 10 (13.5%) patients were alive at 1 year, 10 (13.5%) patients were alive at 2 years and 5 (6.5%) patients were alive at 5 years. 11 (14.47%) patients had diabetes at the time of diagnosis of pancreatic cancer. 5 (6.5%) developed one or more deep vein thrombosis (DVTs) after the diagnosis of PC. Diabetes was present in 15 (19.7%) for an average duration of 19 months. Only 4 (26.6%) out of 15 patients were on insulin therapy before the diagnosis of pancreatic cancer. Six additional patients (an increase of 7.93%) developed diabetes after the diagnosis of pancreatic cancer. 13 (18.9%) of the 21 patients required insulin therapy after the diagnosis of pancreatic cancer. As many as 27 (35%) patients opted for hospice care after the diagnosis of pancreatic cancer. Whipple’s procedure or exploratory debulking surgery of the tumor was performed in 33 (43%) patients. 29 (38.1%) patients received Gemcitabine/carboplatin/5 FU based chemotherapy.

Conclusion
We found that the incidence of Insulin-dependent diabetes increased in patients diagnosed with pancreatic cancer.

Key words
Pancreatic Cancer; Diabetes; Insulin .

Introduction
Pancreatic cancer (PC) is an exceptionally aggressive malignancy. It is the fourth leading cause of cancer-related mortality in the United States (1). Most people die within the first year after being diagnosed with pancreatic adenocarcinoma and the five year survival is around 5% among these patients (2). Globally this malignancy accounts for 250,000 deaths each year (3). These grim statistics are due to the advanced presentation of this malignancy in a majority of these patients at the time of diagnosis. Eighty percent of patients initially present with a stage not amenable to surgery, whereas the remaining twenty percent develop metastatic disease within the ensuing year (4,5). It is therefore imperative to study the risk factors and the implications associated with this lethal malignancy. Both diabetes and a high serum glucose levels have been associated with an increased risk of pancreatic cancer (6-9). In the present study we specifically aim to look at the hypothesis that the insulin requirements increase after the incidence of pancreatic cancer patients.

Materials and Methods
The cohort was established by identifying all males and females in the Danish Central Hospital Discharge Register who were hospitalized with diabetes as a primary or a secondary diagnosis during the years 1977 through 1989. From 1977 through 1986, these individuals were identified by International Classification of Diseases (ICD)-8 code 250 for diabetes (10), and, from 1987 through 1989, by revised codes from the Danish National Board of Health that distinguished IDDM and NIDDM. The cohort entry date was defined as the first day of the month after the initial hospital discharge in which diabetes was identified.

Results
82 patients were identified from the University of Florida Cancer Registry from the year 2000-2006. Complete data was available on 76 patients. Mean age at diagnosis was 66.4 years. 53 (69.7%) were African American, 23 (30.26%) were white. There was an equal male/female distribution of 1:1.07 (43 males; 40 females).
35 (46.0%) patients were smokers. Most common presentation was with obstructive jaundice (33/76 or 43.4%) followed by typical symptoms of weight loss, fatigue, abdominal and back pain (31/76 or 40.78%). In 11 (14.47%) patients, pancreatic cancer was noted as an incidental finding. Staging at the time of diagnosis was available in 76 patients. 48 (63.1%) patients were in Stage 4, 13 (17.1%) patients were in Stage 3, 10 (13.5%) patients were at stage 2 and 5 (6.5%) patients were in Stage 1. 15 (19.7%) patients had diabetes at the time of diagnosis of pancreatic cancer. 5 (6.5%) developed one or more deep vein thrombosis (DVTs) after the diagnosis of PC. Diabetes was present in 15 (19.7%) for an average duration of 19 months. Only 4 (26.6%) out of 15 patients were on insulin therapy before the diagnosis of pancreatic cancer. Six additional patients (an increase of 7.93%) developed diabetes after the diagnosis of pancreatic cancer. 13 (61.9%) of the 21 patients required insulin therapy after the diagnosis of pancreatic cancer. As many as 27 (35%) patients opted for hospice care after the diagnosis of pancreatic cancer. Whipple’s procedure or exploratory debunking surgery of the tumor was performed in 33 (43%) patients. 29 (38.1%) patients received Gemcitabine/carboplatin/5FU based chemotherapy.

Discussion

In the current study we found that more than eighty percent of our patients presented with either stage 3 or 4. Late onset is a hallmark of pancreatic cancer as discussed earlier and plays a significant role in the higher mortality rates associated with this malignancy. Before the onset of PC, diabetes was present in 19.7% of our patient population and most of these patients were managed with oral hypoglycemic agents. Before the diagnosis of pancreatic cancer, only 26.65% of the patient subset with type II Diabetes required insulin therapy, however, after the onset of this malignancy, an additional 7.9 % of the non-diabetic patients were diagnosed with new onset pancreatic cancer associated diabetes. Most importantly, after the onset of PC, 61.9% of this subset required Insulin therapy. About 38% of our patients were treated with chemotherapy agents including 5-Fluorouracil (5-FU), Gemcitabine and carboplatin, none of these could have is typically associated with pancreatic toxicity to explain new onset diabetes. The increased need for exogenous insulin in our patient population suggests that the onset of pancreatic cancer affects the metabolic nomenclature of the human body. This leads to the interesting question: Is it the damaged caused by the pancreatic cancer itself or are there other factors that contribute to the increased insulin dependence seen in our patient population.

The area of pancreatic cancer (PC) and pancreatic cancer associated diabetes (PCAD) is an area of intense study. Several studies have shown that patients with long term diabetes have an increased risk of developing pancreatic cancer. Diabetic patients not only present with an advanced stage pancreatic cancer but stage for stage they also experience shorter survival (10-12). Interesting, low insulin levels in streptozotocin induced diabetes in nude mice models have shown growth retardation in their human pancreatic cancer implants (10-12). Another study in hamsters showed similar results where the researchers lowered the daily insulin secretion in hamsters by decreasing the daily calorie consumption and were successfully able to show growth retardation of pancreatic cancer in these animal models (13,14). Endogenous Insulin up-regulates IGF-I activity and hence acts as a growth factor (15-17).

However, the relationship between diabetes and pancreatic cancer is complicated. While increased insulin levels in the serum may promote the growth and induction of pancreatic cancer (10,14), it is only reasonable to also conclude that the destruction of the islet beta cells of the pancreas from the tumor itself serves as an instigator for new adult onset diabetes (14). In these patients it would be expected that the tumor size in patients who developed diabetes would be larger than in patients who did not develop diabetes. However, multiple studies have shown that this is not the case. Research has shown that the onset of diabetes in pancreatic cancer was not affected by the stage, location or size of the tumor.

Additionally, the level of insulin and C-peptides in PCAD patients is also higher which further argues for adequate insulin production in these patients (18). Another possible hypothesis is the paraneoplastic affect of the pancreatic cancer itself. This hypothesis is supported in multiple studies where tumor resection leads to a complete resolution of the diabetes and glucose intolerance. In one study the author was able to identify MW2030, a peptide, as a potential diabetogenic factor in pancreatic cancer. This has raised hopes for finding a potential serological marker for PCAD in the future (19). Needless to say, the area of pancreatic cancer induced diabetes is not as well studied in the literature (18-22).

Confounding by indication for hospitalization may arise if diseases other than diabetes were the main reason for inpatient care, provided that these diseases are associated with the occurrence of any cancer. To evaluate this possibility, we made separate calculations after a restriction of the cohort to patients with DM as the primary discharge diagnosis and as the only discharge diagnosis, respectively, on the hospital record used for cohort entry.

Several authors have looked into screening protocols; however, none these have gained resolute popularity. In one study Noy et al suggested screening for PCAD in lean patients without family history of diabetes; however, studies by Guollo et al and by Rahul et al showed that one third of patients with PCAD had a family history of diabetes mellitus. Rahul et al also showed that a significantly higher proportion of patients in their study had a higher BMI before the diagnosis of PCAD (18, 23, 24).

Pancreatic cancer is associated with very high mortality with a majority of the patients succumbing to this lethal malignancy within the first year after diagnosis (1-5). In the background of these grim statistics and until better screening and therapeutic tools are discovered that impact mortality in these patients, the exact variation in clinical outcomes associated with long term PCAD remains to be discovered. However, further studies are needed to understand the pathophysiology associated with PCAD in hopes that the discoveries along the way might help influence morbidity and mortality in this patient population.

Conclusion

Our study suggests that Insulin dependent diabetes increases in patients diagnosed with pancreatic cancer. The exact pathophysiology of PCAD remains uncertain, however, one thing is clear: Pancreatic cancer alters the metabolic nomenclature of the human body in ways we do not understand well. We recommend multi-centre, randomized control trials to better understand pancreatic cancer associated diabetes which will not only add to our understanding of the malignancy but it may also open new doors into the morbidity and mortality modifying treatment modalities associated with pancreatic cancer.

References


