Depression and Pancreatic Cancer

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Pancreatic carcinoma, depression, co-morbidity

Abstract
Although pancreatic carcinoma and depression have been linked for years, the prevalence and relationship of these often coexisting diseases are still poorly understood. A clinical gestalt asserts that many patients present with depression before pancreatic carcinoma is diagnosed. Published studies reviewing this issue have found that many patients with pancreatic cancer are depressed. If the definition of depression is broadened to include mild depression in addition to major depression, these numbers increase. This article reviews the literature linking pancreatic carcinoma and depression. (JNCCN 2007;5:113–116)

Pancreatic carcinoma is the fourth leading cause of cancer-related death in the United States. The prognosis is generally poor, with a mean life expectancy of approximately 1 year. The incidence of the disease was 11 per 100,000 in the general public from 1992 to 2002. A clinical correlation of the disease with depression has been identified, although this phenomenon is poorly understood.

During the past 80 years, several studies have shown a higher prevalence of depression in patients with pancreatic carcinoma compared with those with other types of gastrointestinal carcinomas. The range of reported depression varies widely, from 25% to 75%, depending on scales used, when evaluation occurs during the course of the patient’s care, treatments, and many other factors. Multiple competing biologic theories about the cause of increased depression in the context of pancreatic carcinoma are addressed in this article.

History
In the 16th century, Fernel believed that melancholia and hypochondriasis originated in the pancreas. Classic cases and descriptions of depression and pancreatic carcinoma were noted in 1931 by Yaskin, who studied 4 patients with no history of mental or neurologic disorders. These patients first presented with depressive symptoms before another diagnosis was known. All 4 patients were subsequently diagnosed with pancreatic carcinoma: 2 in the head, 1 in the body of the pancreas, and the last presumably in the body. Although these diagnoses were made before newer imaging techniques were available and the study group size was not sufficient to draw a definitive correlation between depression and pancreatic carcinoma, this paper did provide an early glimpse of a potential clinical correlation of diseases. In the description of organic affective syndrome in the 3-volume Comprehensive Textbook of Psychiatry edited by Kaplan et al., pancreatic cancer was associated with depression.

Review of the Literature
Fras and Litin examined psychiatric illness in pancreatic carcinoma, retroperitoneal lymphoma, and lymphoma in other locations. Their study examined 164 patients, 78 of whom had pancreatic carcinoma. Thirteen percent (n = 10) of patients had psychiatric symptoms that were integral to the illness; 3 of these patients were considered to be clinically depressed, with 1 undergoing electroconvulsive therapy before cancer diagnosis. The other 7 were believed to be experiencing anxiety. Another 29% of the group experienced psychiatric symptoms; however, because of the vague descriptions of the symptoms, depression or other psychiatric ailments could not be diagnosed in this study.

Fras et al. performed a prospective comparative study of 125 patients who had carcinoma of either the pancreas or the colon and a control group without cancer but with a gastric diagnosis. Compared with a value
of 46.7 for the control group, the group with pancreatic carcinoma had a mean depression rating scale on the Minnesota Multiphasic Personality Inventory of 63.4, which is categorized as mildly depressed. Of the patients diagnosed with pancreatic neoplasm, 76% also experienced psychiatric symptoms, and half presented with these symptoms before the pancreatic carcinoma was diagnosed. Of the patients with pancreatic carcinoma, 50% experienced depressive symptoms before the preoperative course of the illness. These findings reinforced the clinical link between depression and pancreatic carcinoma.

In a retrospective study, Jacobsson and Ottosson examined 82 patients with sufficient information on 57 cases for analysis and performed an age-matched analysis of carcinoma of the pancreas compared with carcinoma of the stomach. The initial prevalence of mental symptoms was 32% for pancreatic carcinoma and 26% for stomach carcinoma. The symptoms were mainly irritability, weakness, and mild depression for both groups.

Another study, by Joffe et al., examined 21 patients with pancreatic or gastric carcinoma. Fifty percent (6/12) of the patients with pancreatic carcinoma met the Research Diagnostic Criteria for Major Depressive Disorder compared with 0% (0/9) of the patients with gastric carcinoma. Although this incidence of depression with gastric carcinoma differed from that of previous studies, the finding continues to show a prevalence of depression with pancreatic carcinoma. A subsequent psychiatric interview found that 2 of the patients from the depressed group were diagnosed with adjustment disorder secondary to cancer. The authors reported that the depression preceded the diagnosis in many of the patients with pancreatic carcinoma. The addendum showed that of the next 16 patients seen in the clinic, only 3 patients had depression; a 19% (3/16) prevalence.

A larger study examining 111 patients with pancreatic carcinoma and 111 patients with gastric carcinoma found that the average depression score of those with pancreatic carcinoma was 10 using the Profile of Mood States compared with 6 ($P = .23$) for those with gastric carcinoma. No breakout of percent occurred in pancreatic patients with full major depression symptoms.

Another study analyzed pain and depression in pancreatic carcinoma to determine the correlation. Of the 138 patients examined, 38% had a Beck Depression Inventory (BDI) greater than 15, which suggested high levels of symptoms. The average for the patients with pancreatic carcinoma was 13.2 with a standard deviation of 7.5. Another finding was that moderate or great pain showed a high correlation with poorer quality of life and depression.

A case report by Passik and Roth showed that panic attacks preceded the diagnosis of pancreatic carcinoma. Although anxiety and depression precede the diagnosis in other case reports, this was one of the first to note an occurrence of panic attacks.

A large study by Zabora et al. examined 4,496 patients with 14 different carcinoma diagnoses, and found that the 112 patients with pancreatic carcinoma had the highest mean score for both depression and anxiety. The percent of patients with pancreatic carcinoma and distress as evaluated by the Brief Symptom Inventory was 36.6%. This study reinforced an earlier idea that depression scores, whether the depression was mild or moderate, for patients with pancreatic carcinoma were higher than those for patients with other carcinomas.

A recent longitudinal study examined pancreatic carcinoma and depression to help prevent recall bias. Using insurance claims data, Carney et al. found that 1% of patients who filed mental health claims were later diagnosed with pancreatic carcinoma compared with 0.6% of patients who did not file mental health claims. This study used data from Wellmark Blue Cross/Blue Shield of Iowa and South Dakota, and was limited by the reporting of depression by primary care providers and not by research criteria. The median number of days to pancreatic cancer diagnosis was 553 (range, 44 – 1531). These claims data seem to support the theory that depression precedes the diagnosis of pancreatic carcinoma.

A recent retrospective study by Sheibani-Rad and Velanovich examined 258 patients to determine if depression was a prognostic indicator for survival. Depression was considered positive during the chart review if the patient was diagnosed with depression by a mental health provider. Although depression was present, it was not correlated with survival. Of the patients in the cohort, 21% ($n = 54$) had depression. No examination for depression was performed after pancreatic cancer was diagnosed.

Of patients with both pancreatic carcinoma and depression, no more than 300 have been studied in the past 60 years according to the Medline literature.
In the past decade, the correlation of the 2 diseases has been reviewed more than it has actually been studied.18–22

**Treatment**

A review of psychiatric treatments23 summarizes the possible complications with existing cancer treatments and proposed mechanisms associating depression with pancreatic cancer. Existing literature focuses on depression and trying to improve the daily activities or quality of life in patients with pancreatic carcinoma.

**Biologic Mechanisms**

Although pain has been proposed as a correlative finding for patients with depression and pancreatic cancer, adjustment disorder has also been related to the diagnosis. Because depression tends to precede the diagnosis of pancreatic carcinoma in a large number of patients, researchers have attempted to explain the depression in biologic terms.

Jacobsson and Ottosson6 proposed several biologic mechanisms. The first was an increase of 5-hydroxyindolacetic acid (5-HIAA), a metabolite of serotonin, in urine and a high concentration of 5-hydroxytryptophane (5-HTP) or 5-hydroxytryptamine (5-HT) in some tumors.

Joffe et al.12 also proposed an increase in 5-HIAA as a link to depression. The reason for the proposed biologic mechanism is the fact that depression has been reported to be treatment refractory until the tumor is excised.

Holland et al.13 proposed a paraneoplastic syndrome that could alter mood, pointing to neuropeptides mediated by 1 of 2 different methods: 1) antibodies are induced against a protein released by cancer cells and then bind to receptors for serotonin by blocking them, or 2) antibodies could stimulate the production of anti-idiotypic antibodies that would act as receptors for serotonin and reduce synaptic availability.

Shakin and Holland4 reviewed all proposed biologic mechanisms and evaluated the evidence behind the mechanisms, which is beyond the scope of this article. Most of the proposed mechanisms were based on the understanding of depression from the mid-1980s. Although serotonin is still believed to be involved with the pathway in the brain involved with depression, no current studies measure 5-HIAA in the urine as a secondary metabolite. Although the mechanisms behind depression have changed, the proposed theories linking pancreatic cancer with depression have not.

**Conclusions**

Depression and pancreatic carcinoma have been clinically associated. Although many other cancers have been associated with depression,7 depression associated with pancreatic carcinoma sometimes occurs before the cancer is diagnosed. This comorbidity has been acknowledged for more than 80 years, but we still have a poor understanding of the true prevalence of the 2 diseases and their mechanisms. The range is large, with one study showing up to 75% of patients with psychiatric symptoms8 and another showing 19% of patients with depression and pancreatic cancer.9 Patients who are diagnosed with pancreatic cancer tend to have a more depressed mood than other comparative groups. Additional prospective studies must be performed to fully evaluate the correlation and mechanism of pancreatic cancer and depression. Although pain has been examined as a correlate of depression, to improve prevention and treatment, additional studies must also be conducted to better understand this correlation.

**References**


