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Early Detection of Pancreatic Cancer

The Role of Depression and Anxiety as a Precursor for Disease

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Receiving a diagnosis of cancer is known to cause depression in the patient due to the challenges and uncertainty this diagnosis brings. Anecdotal reports of depression before a cancer diagnosis have prompted researchers to consider depression as a possible early signal that there is a disease process at work in the body. The depression-before-diagnosis relationship is particularly notable in pancreatic cancer, which has very few symptoms and frequently is a systemic disease at the time of detection. A review of the literature substantiates that depression and anxiety may be potential precursors to a pancreatic cancer diagnosis. Studies have started to look more closely at this link, with an eye to developing a testable marker for pancreatic cancer.

It is important that medical and mental health professionals are aware of the pancreatic cancer-depression relationship, particularly sudden-onset depression and anxiety in people who have never experienced this condition before, so that the cancer can be identified and treated at an earlier stage. This editorial addresses the role of depression and anxiety as a precursor to cancer and encourages further research on both the biomarker and mental health aspect of pancreatic cancer.

DIAGNOSIS OF PANCREATIC CANCER

Pancreatic cancer is the third leading cause of cancer death, with a 5-year relative survival rate of 9%.¹ Approximately 88% of individuals diagnosed with pancreatic cancer are aged 55 years and older.² The disease is potentially curable only by surgery to remove the tumor. Although pancreatic cancer is believed to develop slowly over an extended period,³ symptoms of the disease generally present only 10 weeks before diagnosis. Most patients are diagnosed when the cancer is in its advanced stages — after it has spread beyond the pancreas. With earlier detection, survival rates are reported to improve significantly.⁴

There are many reasons pancreatic cancer is challenging to diagnose early. Because the pancreas is located deep in the body, a tumor is hard to palpate on examination. Symptoms caused by a tumor are vague and similar to symptoms from many other conditions. Before being diagnosed, patients may lose weight, feel nauseous, have indigestion or pain when they eat, have stomach or back pain, suffer from fatigue, or develop diabetes. All these symptoms can have other causes. Often, people do not see a doctor until the bile duct is blocked. Bile duct blockages produce unique symptoms, including jaundice, dark-colored urine, and light-colored stool. Whether extreme pain or symptoms such as jaundice send a patient to the doctor, by that point, the cancer has metastasized.

Some individuals are considered to be at high risk of developing pancreatic cancer. This includes individuals with a family history of 2 or more close relatives with the disease; carriers of certain genetic mutations, including BRCA1 and 2, PALB2, CDKN2A (FAMMM syndrome), ATM, STK11 (Peutz-Jehgers syndrome), and Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer, or HNPCC); and people with chronic pancreatitis or pancreatic cysts.⁴ In addition, new-onset diabetes has been identified as a possible clue to a growing pancreatic tumor.^{5,6} Approximately 10% of pancreatic cancer cases are due to genetic predisposition, with 7% from familial pancreatic cancer and 3% hereditary cancer syndromes. However, most people who develop pancreatic cancer do not fall into these categories.⁷ There are also nongenetic risk factors for developing sporadic pancreatic cancer. These include age, history of diabetes, obesity, cigarette smoking, and excessive alcohol consumption.¹

A way to intercept this cancer earlier is desperately needed. Current screening techniques involve expensive scans and invasive tests, which are economically unfeasible. A cost-effective approach to screening would use a combination of biomarkers and imaging.⁸ Developing a screening protocol is

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currently a major area of research. Scientists are investigating multiple aspects of the disease, searching for biomarkers in the blood, saliva, urine, and circulating cells as well as improving imaging techniques.^{4,9}

One area that deserves closer examination is the relationship between pancreatic cancer, depression, and anxiety. Many studies have looked at depression after a cancer diagnosis. However, other studies have indicated that patients report onset of psychiatric symptoms before a pancreatic cancer diagnosis. A literature review clarifies this relationship and points to a possible direction for further research.

RELATIONSHIP BETWEEN CANCER, DEPRESSION, AND ANXIETY

According to data published in 2017 by the Anxiety and Depression Association of America, 6.7% of the generalized US population older than 18 years experiences at least 1 major depressive order in a given year. It is not uncommon for some individuals with depression to also suffer from anxiety, which impacts approximately 18.1% of the population every year.¹⁰ Depression is known to occur in between 15% and 30% of cancer patients, a rate that is 3 to 5 times that of the general population. It is also believed that the reported rate of depression may be low because there are so few longitudinal studies.¹¹ Cancer patients and their families are vulnerable to depression because they often experience significant physiological, psychological, and economic stressors.¹² For similar reasons, anxiety can manifest in cancer patients at various times during diagnosis and treatment.

Although psychosocial distress may be a reaction to the disease and worry about the effectiveness of treatment, increasingly, it is believed to be related to the disease process. There is a particular focus on the role of inflammation in depression. Studies show that in some people, inflammation can cause depression, and depression can enhance inflammation, in a bilateral relationship.¹³ Major depression has been associated with inflammatory biomarkers in blood such as cytokines including interleukin (IL)-6. These cytokines are thought to be functionally active in that they cross the blood-brain barrier as evidenced by increased blood and cerebrospinal fluid levels of IL-6. These inflammatory cytokines are likely to be mediators of depression through their influence on metabolism of neurotransmitters, neuroendocrine function, and neural plasticity.¹⁴

Activating the immune response, which releases immune cytokines, is a risk factor for developing depression along with cancer. The concentration of the cytokine IL-6 in plasma has been found to be greater in cancer patients with depression when compared with cancer patients without depression and to healthy people.¹¹ Similarly, a comparison of people with depression alone versus pancreatic, esophageal, or breast cancer patients with depression found higher levels of IL-6 in the cancer patients with depression.¹⁵ Other findings suggest that KRAS mutations¹⁶ have been found to be associated with depression severity and higher rates of probable depression in older metastatic colorectal cancer patients.¹⁷

DEPRESSION AND ANXIETY AFTER A DIAGNOSIS OF PANCREATIC CANCER

Researchers have long noted that depression and anxiety are common in pancreatic cancer patients. When patients with newly diagnosed advanced gastric or pancreatic cancer were assessed for depression, the patients with pancreatic cancer were found to have a greater incidence of depression and related symptoms,¹⁸ which can contribute to a lower quality of life.¹⁹

According to 1 study, pancreatic cancer patients experience depression at a notably higher rate than patients with other gastrointestinal cancers, affecting as many as 50% to 78% of patients.²⁰ In another study, 22 patients with confirmed pancreatic cancer diagnoses were screened for depression, anxiety, and sleep disturbance over a 6-month treatment period. The results showed 4 patients had moderate to severe symptoms of these disorders, whereas 3 others showed symptoms at a poststudy follow-up. There were additional patients who had mild anxiety and depression symptoms.²¹

In a study of 304 pancreatic cancer patients, a greater percentage reported symptoms of distress, depression, somatization, and anxiety when compared with patients with other cancers. Men in particular were more likely to report higher levels of depression. Although these patients may have been responding to the poor prognosis, the researchers indicated there may be poorly understood underlying metabolic causes related to the cancer.²² Other studies have proposed that something related to the tumor causes depression in patients with advanced pancreatic cancer.¹⁸ Survival possibilities do not seem to be a factor, and there is no relative evidence that how a person copes with adversity influences survival of this cancer.²³

In the current issue of this journal, Bauer et al²⁴ present findings from a systematic review of research on quality of life of patients with pancreatic cancer. Psychological wellbeing was identified as an area of particular strain.

DEPRESSION AND ANXIETY AS PRECURSORS TO CANCER

Depression and anxiety as precursor symptoms to a physical illness have become increasingly accepted. This pairing recently appeared as the subject of a 2017 *New York Times* science article, which includes pancreatic cancer among the conditions that have depression as an early symptom.²⁵

One of the strongest links between mental disorders preceding a cancer diagnosis was shown in a 2016 study from Sweden. The study included 300,000 cancer patients and more than 3 million cancer-free individuals (controls). The researchers found an increased risk of psychiatric illness nearly a year before the cancer was diagnosed. Mental disorder diagnoses peaked shortly after cancer diagnosis. In addition, the mental disorder diagnosis rate elevation was stronger for cancers with poor prognoses.²⁶

A large group of participants drawn from national health surveys of England and Scotland participated in a long-term study examining the relationship between psychological distress and death from cancer. More than 163,000 men and women, cancer-free and older than 16 years, joined at the start of the study. They self-reported psychological symptoms while allowing their health records to be tracked by the researchers. The results show evidence that psychological distress might have some predictive capacity for certain cancers, including pancreatic cancer.²⁷

DEPRESSION AND ANXIETY PRECEDING A DIAGNOSIS OF PANCREATIC CANCER

Since a 1931 report by Yaskin et al,²⁸ researchers studying pancreatic cancer have noted that depression frequently occurs with this disease, positing the possibility of a physiological process that creates a reciprocal interaction. Reports from 1967,²⁹ 1986,³⁰ 1999,³¹ and 2008³² have elucidated different aspects of the relationship, from a loss of ambition to the presence of anxiety and panic attacks to symptoms considered atypical of depression. Two literature reviews — one from 1993³³ and the other from 2014³⁴ — reported that between 33% and 45% of pancreatic cancer patients reported psychiatric symptoms before medical symptoms.

In fact, many of the symptoms attributed to depression — loss of appetite, weight loss, and fatigue — may also be early signs of cancer.³⁰ According to the 1967 study, in up to half of the pancreatic cancer patients with psychiatric symptoms, those symptoms were the first indication of the illness and preceded the onset of the first somatic symptoms by a mean of 6 months.²⁹

Further evidence of the relationship between pancreatic cancer and psychiatric symptoms is presented in a study that used insurance claims data from Iowa and South Dakota gathered over a 4-year period.³⁵ The purpose behind using data from insurance claims was to eliminate any bias from self-reporting. The researchers identified all people who filed insurance claims for mental health disorders and/or pancreatic cancer. The mental health claims study cohort were people who had mental health claims before filing pancreatic cancer claims; the controls were people with pancreatic cancer who never filed mental health claims. Men who had filed mental health claims were more likely to develop pancreatic cancer, with claims being filed on an average of 1.5 years before pancreatic cancer diagnosis. This gap suggests that depression is unlikely to mask physical symptoms of pancreatic cancer.³⁵

A study including pancreatic cancer patients from Memorial Sloan Kettering Cancer Center in New York and healthy controls found that 42% of patients lost at least 10% of their weight; 15% of the cases reported a new diabetes diagnosis within 3 years of their pancreatic cancer diagnosis. In addition, 5% of the patients in the study reported fatigue and depression in the year before the pancreatic cancer diagnosis, which was twice the rate of the controls.³⁶

THEORIES WHY DEPRESSION, ANXIETY, AND PANCREATIC CANCER ARE LINKED

As the relationship between depression and anxiety preceding a pancreatic cancer diagnosis becomes more accepted, researchers have focused on the nature of this relationship. However, there is as of yet no real agreement or understanding of how common the co-occurrence of depression, anxiety, and pancreatic cancer is and what may be the underlying driving mechanism.³⁷ An early literature review postulated possible causes, concluding that a tumor-related paraneoplastic syndrome producing a false neurotransmitter was the most likely cause capable of altering mood.³⁸

A number of different approaches have been taken to study the link, including immunological, hormonal, paraneoplastic, and biochemical.³⁹ There is speculation that the changes in mood and anxiety levels could be related to the functions of the pancreas, which secretes hormones, neurotransmitters, digestive enzymes, and bicarbonate.⁴⁰

Among the theories considered are that depression may be a symptom of a growing pancreatic tumor or that depression might predispose a person to developing pancreatic cancer through its weakening effect on the body's immune system.⁴¹ Another theory posits the main link between depression and cancer in general as immune or cytokine dysregulation. Depression may increase the subsequent risk for developing cancer, thus introducing a bidirectional relationship. However, there are other factors to consider in the cancer-depression relationship — age, smoking, alcohol use, obesity, and family history.³⁹ One study found evidence of elevated proinflammatory cytokine production in pancreatic cancer, and a particular association between higher IL-6 levels, depression, and pancreatic cancer.⁴²

The article by Bettison et al⁴³ in this journal clarifies this theory as well as other approaches and more fully examines

the mechanisms identified between psychological distress and pancreatic cancer.

CONCLUSIONS

There is evidence that for some patients, psychiatric symptoms may provide an earlier clue to the presence of a growing pancreatic tumor. Yet, depression and anxiety are very general symptoms and not something that can drive testing for pancreatic cancer by itself. Not everyone who has depression or anxiety harbors the disease. However, wider knowledge of this link may drive a closer examination for other symptoms and lead to earlier interception of pancreatic cancer. Because earlier diagnosis potentially results in an improved prognosis for patients, it is expedient then to examine how our current knowledge can be used to support the diagnosis of this cancer at an earlier and more treatable stage.

In 2016, guidelines for screening of depression were published by The United States Preventive Services Task Force (USPSTF), an independent panel of experts in primary care and prevention that systematically reviews the evidence of effectiveness and develops recommendations for clinical preventive services.⁴⁴ Specifically, the guidelines recommend screening for depression in the general adult population, with adequate evidence that there is almost no harm to patients in doing so. Commonly used depression screening scales include the Patient Health Questionnaire, the Hospital Anxiety and Depression Scales, and the Geriatric Depression Scale for older adults. All screening results that indicate the presence of depression should then lead to additional assessment that considers how severe the depression is, along with any other coexisting psychological issues, alternate diagnoses, and medical conditions as well as treatment options.⁴⁴

The USPSTF recommendations provide a framework for a multipronged strategy to untangle the link between pancreatic cancer, depression, and anxiety from both biological and mental health perspectives. First, further research needs to be supported on the underlying pathophysiology of the mind-body connection with regards to depression, anxiety, and pancreatic cancer. The continued study of potentially shared biomarkers, such as IL-6 or KRAS, which is a well-validated driver of pancreatic cancer growth and maintenance and found to occur in 90% of pancreatic carcinomas,⁴⁵ is also critical to exploring the biological processes underlying a depression that may appear before the development of disease symptoms.

Standardized depression and anxiety scales need to be regularly embedded in rigorous, large-sample size prospective studies, particularly in high-risk cohorts such as new onset of diabetes, to verify the link as well as to distinguish anxiety associated with new-onset diabetes diagnoses versus spontaneous cancer-induced depression. Those individuals who score positive for depression and anxiety need to be referred on for further assessment and treatment.

As the occurrence of depression and anxiety before a pancreatic cancer diagnosis becomes more established through research, the best way to integrate this information into clinical practice needs to be determined. For many individuals, primary care providers such as general internists or family medicine practitioners are the first line for diagnosis and treatment for mental health disorders. Most doctors recommend pharmaceutical treatment alone for patients presenting with depression rather than psychological counseling or some combination of the two.⁴⁶ This may lead to insufficient questioning of the patient about the nature of the depression.⁴⁷

Assessment, in the form of a family history or deeper questioning about the depression or anxiety, as recommended by the USPSTF, can provide a clue as to whether the depression

may have roots in another illness that has not yet been diagnosed. General practitioners and mental health professionals need to be educated that these symptoms are critically important when reported by an individual who has not had depression or anxiety previously, is older than 50 years, and may be at high risk for pancreatic cancer (eg, familial, new onset of diabetes). In those situations, referral to a mental health practitioner who can further assess the patient may be as important as providing a prescription that can help alleviate the depression or anxiety.

Earlier diagnosis of pancreatic cancer has proved to be challenging, and progress has been slow. Studies supported by the government, industry, research institutions, and philanthropy are now collaborating to collect serum samples, identify biomarkers, and develop noninvasive imaging to confront this disease, giving hope that in the not too distant future, there will be consensus guidelines for earlier interception. In the meantime, an estimated 53,670 individuals were diagnosed with pancreatic cancer in 2017, and an estimated 43,090 lost their lives to the disease.¹

Pancreatic cancer has mocked and teased us all for too long. We need to expand our understanding of the disease, appreciate its holistic impact on the body and mind, and not overlook the subtle clues it communicates. Depression and anxiety as potential precursors for disease presents 1 more piece of a complex puzzle to ensure timely diagnosis of pancreatic cancer and to improve survival.

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