

## Pancreatic Cancer

Pancreatic cancer is the fourth leading cause of cancer death in the United States, accounting for approximately 30,000 deaths each year (Michaud DS 2004). Worldwide, more than 200,000 people die from this cancer each year.

Little is known about the causes of pancreatic cancer. The disease is difficult to diagnose in its early stages, as it presents few symptoms and there are few tests to screen for it. As a result, most patients have incurable disease by the time they are diagnosed. Fewer than 5 percent of pancreatic cancer patients survive five years beyond diagnosis of the disease. Surgery is the only hope for cure; however, due to the aggressive nature of pancreatic tumors, only 5 percent to 20 percent of patients are candidates for surgery (Cleary SP et al. 2004). Chemotherapy and radiation therapy produce only minor increases in survival rates. Conventional medicine's inability to treat pancreatic cancer effectively is illustrated by the fact that more than 90 percent of patients die within 12 months of diagnosis. Along with lifestyle changes and nutritional approaches, novel therapeutic strategies are needed for the treatment of pancreatic cancer.

### ABOUT THE PANCREAS

The pancreas is a pear-shaped gland located across the back of the belly, behind the stomach. It comprises the exocrine pancreas, which produces pancreatic enzymes that help break down carbohydrates, fats, and proteins, and the endocrine pancreas, which produces hormones such as insulin and glucagon that regulate how the body stores and uses food.

### *Risk Factors for Pancreatic Cancer*

- Age, sex, race, and ethnicity. The disease is more common in the elderly and among men, and there is a higher incidence rate among African-Americans (Ghadirian L et al 2003).
- Smoking (Lowenfels AB et al 2002; Michaud DS 2004).
- Exposure to chemicals such as gasoline, petroleum products, and DDT (Alguacil J et al 2003; Hoppin JA et al 2000; Simon B et al 2001).
- Inherited pancreatic disease and inherited breast cancer (Cowgill SM et al 2003; Ghadirian P et al 2003; Lowenfels AB et al 2004).
- Chronic pancreatitis and diabetes mellitus (Truninger K 2000).
- Insulin resistance (Berrington de Gonzalez A et al 2003).
- Diet: excess calorie intake; high intake of saturated fats and oils, including omega-6 fatty acids, meat, and dairy products; and high intake of fried foods, carbohydrates, cholesterol, salt, nitrites from animal products, and nitrosamines (Coss A et al 2004).

About 95 percent of pancreatic cancers begin in the exocrine pancreas, where enzymes are produced. The remaining 5 percent are cancers of the endocrine pancreas, where hormones are produced; these are also called islet cell cancers. Typically, pancreatic cancer spreads first to nearby lymph nodes, then to the liver and, less commonly, the lungs. It can also directly invade surrounding organs such as the upper region of the small intestine, stomach, and colon.

### ALTERATIONS OF FUNCTION IN PANCREATIC CANCER

Pancreatic cancer can alter the normal function of the pancreas by:

- Creating a deficiency of pancreatic enzymes, bicarbonate, and bile salt.
- Causing poor absorption of nutrients from food.
- Impairing the use of pancreatic enzymes.

The activity of pancreatic enzymes is impaired by an acidic environment, which is partly determined by dietary intake. Each day, the exocrine tissue secretes about 2 liters of bicarbonate (a buffer) to neutralize stomach acid in the small intestine. Reduced bicarbonate levels create an acidic microenvironment that weakens the activity of pancreatic enzymes. Some evidence suggests that antacids, alkaline diet, and essential fatty acids may be beneficial in treating pancreatic cancer (Nakamura T et al 1995; Ohta T et al 1996; Ravichandran D et al 1998).

## CAUSES OF AND RISK FACTORS FOR PANCREATIC CANCER

While the exact cause of pancreatic cancer is not known with certainty, several factors—including smoking, nutrition, glucose levels, hormones, and genetics—are thought to be involved in its initiation and development.

**Smoking.** Smoking is a major risk factor, accounting for 25-30 percent of all cases. Heavy smokers are two to three times more at risk for cancer than are nonsmokers (Lowenfels AB et al 2002). Several studies have observed a reduction in pancreatic cancer risk within a decade after smoking cessation (Michaud DS 2004).

**Nutritional influences on pancreatic cancer.** DNA damage caused by exposure to free radicals has been found in human pancreatic tissues (Uden S et al 1992). In pancreatic cancer cells, antioxidant levels are much lower compared to those in non-cancerous pancreatic cells. Nutritional supplements such as alpha-tocopherol (Ferreira PR et al 2004; Hernandez J et al 2005; Rautalahti MT et al 1999), ascorbic acid (Zullo A et al 2000), zinc (Ertekin MV et al 2004; Prasad AS et al 2004; Uden S et al 1992), and selenium may be beneficial in elevating antioxidant levels (Zhan CD et al 2004).

**Glucose levels and pancreatic cancer.** Abnormal sugar metabolism, diabetes (DeMeo MT 2001; Gapstur SM et al 2000), and foods that elevate after-meal blood sugar levels are associated with increased pancreatic cancer risk in individuals with insulin resistance (Michaud DS et al 2002). Increasing soluble fiber intake has been shown to improve after-meal glucose levels and insulin response in healthy subjects (Aller R et al 2004; Lu ZX et al 2000). Thus, supplemental fiber may help to stabilize glucose levels (Rayes N et al 2002; Tsai AC et al 1987).

**Phytoestrogens.** Evidence suggests that the increased incidence of pancreatic cancer in Western nations may be related to the relatively low dietary content and qualities of naturally occurring plant hormones (phytoestrogens) (Stephens FO 1999). Daidzein, a phytoestrogen found in soybeans, chickpeas, and dietary supplements, has been shown to slow the growth of pancreatic cell lines (Guo JM et al 2004).

**Folate.** Maintaining adequate blood folate levels or increasing folate intake from dietary or vitamin sources may reduce pancreatic cancer risk significantly (Kim YI 1999). In a study of 27,101 healthy male smokers, 157 developed pancreatic cancer during 13 years of follow-up. Those with the lowest folate intake showed a 48 percent increased risk of pancreatic cancer (Stolzenberg-Solomon RZ et al 2001).

**Lycopene.** Data support an association between reduced lycopene levels and pancreatic cancer (Comstock GW et al 1991). In a clinical study, low levels of lycopene, retinol, and beta-carotene were strongly associated with pancreatic cancer (Abiaka CD et al 2001). Tomatoes are a rich dietary source of lycopene, which is also available as a dietary supplement (Ansari MS et al 2004).

**Olive Oil.** Olive oil contains several antioxidants and a protective fat called oleic acid that diminish the risk of cell damage (Owen RW et al 2004) by scavenging free radicals (Alarcon de la Lastra C et al 2001). In a study of 362 pancreatic cancer cases and 1502 controls in Italy, olive oil had a comparatively more favorable impact on pancreatic cancer risk than did other types of fats (La Vecchia C et al 1997).

### ARE HORMONES INVOLVED?

**Testosterone:** A low serum testosterone/dihydrotestosterone (DHT) ratio has been observed in some patients with pancreatic carcinoma (Corbishley TP et al 1986; Robles-Diaz G et al 2001). Based on findings that hormone receptors are contained in human pancreatic adenocarcinomas (Andren-Sandberg A et al 1990) and on experimental studies showing that pancreatic cancer development is influenced by sex hormones (Robles-Diaz G et al 2001), it is possible that hormonal manipulation might be of value in treating pancreatic cancer (Ganepola GA et al 1999). In one study, an anti-androgen was shown to prolong life significantly in patients with inoperable pancreatic carcinoma (Andren-Sandberg A et al 1990).

**Parathyroid hormone-related protein (PTHrP):** PTHrP regulates the growth and division of experimental pancreatic cancer (Grzesiak JJ et al 2004; Grzesiak JJ et al 2005). PTHrP is produced in pancreatic adenocarcinoma tumor specimens, suggesting that it may be a useful marker in monitoring the growth of pancreatic cancer in the body (Bouvet M et al 2002).

### GENETIC AND PROTEIN CHANGES

Genetic damage is highly associated with pancreatic cancer (Shiraishi K et al 2001). People with immediate family members affected by the disease are at increased risk for pancreatic cancer (Rulyak SJ et al 2003) and should consider pancreatic cancer screening if it becomes available.

At least 222 genes are overproduced and active in pancreatic cancer, and may be valuable in discovering novel ways to stop tumor growth (Grutzmann R et al 2003). Readers with neuroendocrine tumors are referred to Genzyme Genetics

(www.genzymegenetics.com) for more information on how to obtain an analysis of genes found in their tumors, which may be beneficial in determining an optimal, individualized treatment plan.

### ***Activation of cancer-associated genes (oncogenes)***

K-ras and HER2/neu are cancer-associated genes (oncogenes) that acquire mutations resulting in the inactivation of genes that typically prevent tumor formation. These include p16, p53, DPC4, BRCA2, and FHIT (Moore PS et al 2003).

**Ras genes.** Ras proteins play a central role in regulating cell growth, multiplication, and life cycle. Mutations in the ras genes can transform normal cells into cancerous cells that grow rapidly and form tumors. Ras oncogene mutations have been identified in up to 95 percent of pancreatic cancers (Brasiuniene B et al 2003). Smoking and alcohol and coffee consumption have been linked with the occurrence of ras mutations in pancreatic tumors (Li D et al 2003).

**Detection of K-ras mutations.** The detection of K-ras mutations may help to predict treatment outcome. K-ras mutations are relatively easy to detect in different human tissues, including blood, intestinal fluid (Wilentz RE et al 1998), pancreatic fluid (Boadas J et al 2001), stool (Caldas C et al 1994), regional lymph nodes and other bodily fluids, and the tumor itself (Brasiuniene B et al 2003).

Ras gene activity can be slowed by:

- Fish oil containing the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Singh J et al 1997).
- Garlic's natural component, diallyl disulfide (Gail MH et al 1998; Singh SV 2001).
- d-Limonene and perillyl alcohol, natural monoterpenes (Chen X et al 1999) from citrus fruits and essential oils.
- Green tea extract containing epigallocatechin gallate (EGCG) (Lyn-Cook BD et al 1999a).
- Black tea extract containing black tea polyphenol (BTP) (Lyn-Cook BD et al 1999a).

Tumor cells with a mutant ras are more difficult to kill with radiation than are cells with normal ras (McKenna WG et al 2003). However, laboratory experiments have shown that the FTI (farnesyl transferase inhibitor) drug L-744,832 makes pancreatic cancer cells with a K-ras mutation more sensitive to the killing effects of radiation (Alcock RA et al 2002). Therefore, the combination of an FTI and radiation may offer therapeutic advantages for those undergoing radiotherapy (Shi Y et al 2005).

**HER2.** HER2 is found in many pancreatic cancers and is associated with poor patient survival rates. In one study, patients with HER2 lived for only 7 months, whereas those without it lived at least 19 months (Lei S et al 1995).

- A flavonoid called apigenin reduces the growth of cancer cells containing HER2 significantly (Way TD et al 2004).
- HER2 can be targeted specifically by the neutralizing antibody drug Herceptin®.

**EGF-R (epidermal growth factor receptor).** In pancreatic cancer cells, EGF-R is turned on and levels are 4-fold higher than in normal healthy pancreatic cells (Friess H et al 1999).

- The green tea polyphenol EGCG has been shown to block EGF-R activity (Liang YC et al 1997), as have luteolin and quercetin (Baker CH et al 2002a).
- Curcumin prevents activation of EGF-R (Korutla L et al 1995).
- Genistein from soy is powerful in reducing levels of EGF-R (McIntyre BS et al 1998) and may disable the EGF-R signaling pathway (Bai J et al 2004).

### ***Important genes turned off in pancreatic cancer***

Compared to other major types of cancer, pancreatic cancer evinces a loss of activity of genes known to suppress tumor development, such as p16, DPC4, BRCA2, and p53.

**p16** is turned off in virtually all pancreatic ductal cancers (Bartsch DK et al 2002; Cowgill SM et al 2003) and in 40 percent to 75 percent of all pancreatic cancers.

**DPC4** is absent from approximately 50 percent of pancreatic cancers and is associated with more-invasive cancer growth (Cowgill SM et al 2003).

**BRCA2** mutations have been clearly associated with pancreatic cancer development (Naderi A et al 2002).

**p53:** Because p53 is involved in repairing damaged DNA, when this gene is inactive (turned off) or malfunctions, damaged DNA is able to proliferate and form cancerous cells (Berrozpe G et al 1994). Nutritional supplements known to change levels or restore function of the p53 gene include:

- Red grape seed proanthocyanidins (Joshi SS et al 2001).
- Folate (Kim YI et al 2001).
- Phytochemicals such as genistein from soy (Lian F et al 1999), indole-3-carbinol (I3C) from cruciferous vegetables, and the green tea polyphenol EGCG (Kamdare M et al 1998).

**Regulation of Transcription Factors.** A transcription factor controls whether a particular gene is turned on (active) or turned off (inactive). Transcription factors can be activated or deactivated selectively by other proteins, often as a final step in the process of transmitting their signals. The presence and activity of these factors can differ in normal and cancerous tissues.

**STAT3** is a dormant transcription factor activated in pancreatic cancer but not in normal pancreatic tissue.

- Nutritional agents such as I3C and genistein inhibit STAT3 from functioning (Lian JP et al 2004).

**NF-kappa B** is another transcription factor activated in human pancreatic cancer but not in normal pancreatic tissue. Blocking NF-kappa B activity prevents cancer invasion and spread (metastasis) in animals with tumors. Furthermore, preventing NF-kappa B activity reduces levels of molecules involved in tumor blood-vessel development, thereby retarding tumor growth and slowing cancer spread (Fujioka S et al 2003).

- Genistein and curcumin both reduce NF-kappa B activation (Li L et al 2004; Li Y et al 2004).

### ***What You Have Learned So Far***

- When pancreatic cells do not die when they should, pancreatic cancer results (called carcinoma of the pancreas or, rarely, islet cell tumor).
- Pancreatic cancer has the lowest five-year survival rate of any cancer.
- Conventional treatment does not appreciably extend survival.
- Surgery is the only hope for cure.
- Smoking, obesity, exposure to chemicals, genetics, and eating red meat, refined sugar, and fried foods increase pancreatic cancer risk.
- Diet and lifestyle modifications may improve outcomes.
- Genetic analysis of tumors provides information for customized treatment.

### **POSSIBLE SIGNS AND SYMPTOMS OF PANCREATIC CANCER**

- Jaundice (yellowing of the skin and whites of the eyes) due to blockage of the bile duct or liver malfunction.
- A gnawing pain from the stomach to the back.
- Unexplained weight loss from malabsorption of nutrients or loss of appetite.
- Fatigue or chronic tiredness.

### **LABORATORY TESTING**

Early diagnosis of pancreatic cancer is difficult, even with recent advances in diagnostic methods. Symptoms develop gradually and steadily, and are often present for many months before diagnosis. Physicians typically use a range of imaging studies to confirm the diagnosis (see sidebar on "Diagnostic Imaging"). The development of improved early-detection methods is essential (Brand R 2001). No standard for pancreatic cancer screening exists, but strategies employing endoscopic, radiologic, and molecular methods to screen high-risk individuals are under investigation (Konner J et al 2002). Tumor markers (substances in the body that indicate the presence of tumors) do not permit early diagnosis of pancreatic cancer, but on follow-up are used to indicate the presence of tumors. Endoscopic ultrasound has been used to detect abnormal pancreatic cells in family members of pancreatic cancer patients; in high-risk patients, it has revealed cystic masses that were not detected by spiral CT scan (McBride 2004; Pezzilli 2004; Rulyak SJ et al 2004).

#### ***Blood Tests***

CA 19-9 (carbohydrate antigen 19-9) is the mainstay tumor marker and is ordered when pancreatic cancer is suspected, particularly

if the patient shows signs of jaundice (yellowing of the skin). CA 19-9 levels match the course of the disease following surgery, chemotherapy, or radiotherapy, normalizing or decreasing soon after treatment (Lamerz R 1999). Additional diagnostic methods are required because this test is only 70 percent sensitive and 87 percent specific for pancreatic cancer.

- Among the serum tumor markers that may be measured by a blood test and can be used in conjunction with other tests for the diagnosis and follow-up of surgically treated pancreatic cancer are CA19-9, CA-50, CA72-4, and CA242 (Jiang XT THZSC 2004).
- High platelet counts may be associated with a poor outcome and a shortening of the disease-free survival interval (Suzuki K et al 2004).

### ***Tumor Markers***

In a prospective study of 58 patients with pancreatic cancer, 40 with alcoholic pancreatitis, and 40 healthy controls, CA 19-9, tissue plasminogen activator (TPA), and carbohydrate antigen 50 (CA-50) were found to be useful in identifying differences between pancreatic cancer and chronic pancreatitis. The specificity of TPA, CA 19-9, and CA-50 in differentiating between pancreatic cancer and chronic pancreatitis was 87.5 percent, 90 percent, and 95 percent, respectively, with a sensitivity of nearly 90 percent (Irigoyen Oyarzabal AM et al 2003).

**Assessment of pancreatic function.** In pancreatic cancer, abnormal digestion associated with inadequate pancreatic enzymes and function (insufficiency) can occur (Bruno MJ et al 1995a; Grant AG et al 1978). When pancreatic enzyme levels fall below 1 percent to 2 percent of normal, poor nutrient digestion and incorporation occur. Poor digestion can cause significant weight loss, nutritional deficiencies, and foul-smelling or greasy bowel movements. It is also associated with changes in gastrointestinal function, such as changes in acid-base balance, bile acid metabolism, stomach emptying, and motility of the intestine.

**Tests for pancreatic enzyme function.** These tests are sensitive for moderate-to-severe pancreatic insufficiency, but are of limited value in mild pancreatic impairment.

- Bicarbonate secretion is probably the single most useful measure of pancreatic enzyme function (Ochi K et al 1997). Indirect estimation can be done via the 72-hour fat balance test, which determines fat losses as a percentage of daily fat intake.
- Measuring the activity of pancreatic chymotrypsin (a pancreatic enzyme).
- A test in which oral fluorescein dilaurate is broken down by esterase, a pancreatic enzyme.
- Fecal elastase-1 is a simple, non-invasive, and robust test (Sonwalkar SA et al 2003) of fat balance in the body.
- Cholesteryl-[14C]octanoate breath test (Bruno MJ et al 1995b).

With enzyme supplementation (for example, with pancrelipase, enteric-coated microspheres), body weight loss and biochemical indices of malnutrition can be greatly improved (Braga M et al 1988).

### **Tests for pancreatic hormone function:**

- Insulin: Fasting blood sugar levels and an oral glucose tolerance test (OGTT) (Yamaguchi K et al 2000).
- Measurement of hormone levels (insulin, glucagon, somatostatin, and pancreatic polypeptide) after a meal (Schusdziarra V et al 1984).

### **Diagnostic Imaging**

- **CT (computed tomography).** A spiral CT detects tumor presence and cancer spread, and assesses the feasibility of surgically removing the growth (Dimagno EP et al 1999).
- **Ultrasound.** If the patient is jaundiced, an ultrasound (US) will be performed.
  - **EUS (endoscopic ultrasonography)** can differentiate between pancreatic cancer and pancreatitis (Levy MJ et al 2002), and can detect pancreatic lesions of less than 20 mm in size and small islet cell tumors of less than 10 mm (Yamao K et al 2003).
  - **IDUS (intraductal ultrasonography)** is useful in detecting carcinoma in situ, identifying small tumors, differentiating non-cancerous (benign) from cancerous (malignant) cases, and assessing cancer spread (Yamao K et al 2003).
- **MRI (magnetic resonance imaging).** MRI between the chest and hips has a sensitivity of 100 percent (Schima W et al 2002). Enhanced MRI offers improved detection of small pancreatic spread and liver metastases.
- **PET (positron emission tomography).** PET with 18-fluorodeoxyglucose (18-FDG PET) is an experimental technique that can detect cancers as small as 7 mm in diameter and distant cancer spread in approximately 40 percent of cases. False positives (tests indicating that cancer is present when it is not) can occur in inflamed tissues (Saisho H et al 2004) and in chronic and autoimmune pancreatitis (Higashi T et al 2003).

## **TYPICAL MEDICAL TREATMENTS FOR PANCREATIC CANCER**

Conventional cancer treatments include surgery and various types of radiation therapy and chemotherapy. Apart from surgery, standard treatments do not prolong survival significantly. However, adjuvant systemic chemotherapy using gemcitabine showed some survival benefit in stage IV pancreatic cancer patients. The respective survival rates of the gemcitabine and surgery-only groups were 86 percent and 70 percent at one year, and 50 percent and 12 percent at two years, with a median survival time of 20 months and 14 months. The disease-free interval was improved, and the occurrence of hepatic metastasis was reduced in the gemcitabine group compared to the surgery-only group (Kurosaki I et al 2005).

Experimental treatments under investigation should be explored, including:

- Targeted antibodies (HER2/neu, EG-FR) that bind to unique proteins on pancreatic cancer cells and alert the immune system to attack them (Hansel DE et al 2005; Kim T 2004; Xiong HQ et al 2004b).
- Drugs known as antiangiogenics that prevent new tumor blood vessels from developing, which is necessary for tumor survival (Sangro B et al 2004).
- Drugs known as anti-metastatic agents that prevent cancer from invading healthy tissues (Blumenthal RD et al 2005).
- Vaccines such as Oncophage and GM-CSF (Jaffee EM et al 1998).
- New drugs that were not originally developed for pancreatic cancer treatment but have incidentally been shown to hinder its growth, including drugs that eliminate the activity of the enzymes COX-2 (cyclooxygenase-2) (for example, Celebrex®) and 5-LOX (5-lipoxygenase) (Anderson KM et al 1998b; Crane CH et al 2003; Ding XZ et al 2001; Hennig R et al 2002; Kokawa A et al 2001; Tong WG et al 2002; Tucker ON et al 1999).
- Replenishing the body with pancreatic enzymes that may not be produced because of the cancer may also be a beneficial strategy to consider (Novak JF et al 2005).

### **Surgery**

Only 15 percent of pancreatic cancer patients may be eligible for complete surgical removal of their tumors, a procedure known as a Whipple resection. This is a high-risk procedure with a mortality rate of 15 percent and a five-year survival rate of only 10 percent (Snady H et al 2000). The median survival time for the inoperable 85-90 percent of cases is often only a few months. Management of these cases is based on relieving symptoms (referred to as palliative care).

Various chemotherapy drugs may be used before or after surgery to remove most of the tumor. Chemotherapy combined with radiotherapy often is used in the conventional treatment of pancreatic cancer (Snady H et al 2000).

### **Radiation**

Radiation therapy alone can improve pain and may prolong survival (Goldstein D et al 2004). Precision external-beam techniques are required. For patients with advanced pancreatic cancer, a radiation procedure known as IMRT (intensity modulated radiation therapy) combined with the drug 5-fluorouracil (5-FU) can provide symptom relief with tolerable short-term toxicity (Bai YR et al 2003). Please refer to the Cancer Radiation protocol for information on supporting healthy tissues during radiation therapy.

**Radioimmunotherapy** (RAIT, RIT) is a novel approach in which radiation is delivered to known and unknown tumor sites by chemically linking the radiation source to an antibody (a type of protein) that specifically targets a tumor marker.

- The PAM4 antibody targets the MUC1 mucin produced in more than 85 percent of human pancreatic cancers (Gold DV et al 1994).
- MUC4, another mucin that is overproduced in pancreatic cancer, is associated with cancer that spreads and with altered growth of tumor cells (Singh AP et al 2004). Anti-MUC4 monoclonal antibodies have been developed and may represent a powerful tool for diagnosing and treating pancreatic tumors (Moniaux N et al 2004; Saitou M et al 2005). When mice with pancreatic tumors were treated with a radioiodine-linked antibody, tumors decreased to approximately 15 percent of their initial volume, while untreated tumors grew 16.5-fold over the same period (Gold DV et al 1997).
- A similar radioantibody approach using yttrium-90 as the radiation source in combination with the drug Gemzar® was found to be more effective than either treatment method alone, with minimal toxicity to normal tissues (Gold DV et al 2003).

## **Chemotherapy**

While many chemotherapy drugs have been evaluated, no single drug has produced a significant response rate or greatly improved the average survival rate. One chemotherapy approach for pancreatic cancer is a combination of 5-FU, streptozotocin, and cisplatin (Snady H et al 2000). Understandably, every chemotherapy treatment plan must be individualized according to the type, location, and progression of the patient's pancreatic cancer. Please refer to Genzyme Genetics ([www.genzyme.com](http://www.genzyme.com)) for more information on individual tumor analysis, which may be beneficial in determining an optimal, individualized treatment plan.

Evidence suggests that the proper combination of cell-differentiating agents (agents that convert cancer cells to normal cells) and chemotherapy drugs may slow pancreatic cancer progression (Missiaglia E et al 2005). In order to have a realistic chance of achieving a significant remission (a complete or partial disappearance of cancer), the use of nutritional supplementation together with experimental or investigational therapies, including clinical trials ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)), is highly recommended (Modrak DE et al 2004).

## **Long-Term Survival with Alpha-Lipoic Acid (Intravenous), Multiple Antioxidants, and Low-Dose Naltrexone**

A recent case report describes the long-term survival (>3 years) of a 46-year-old man who was diagnosed with a very aggressive cancer of the pancreas (adenocarcinoma) which had spread to the liver (Berkson BM et al 2006). The patient had a 3.9 x 3.9 cm tumor in the head of the pancreas and 4 tumors in the liver, one of which was 5 to 6 cm in diameter. He was told there was not much that could be done for him, yet he was treated with one round of a typical chemotherapy regimen (Gemzar® (gemcitabine) and Paraplatin® (carboplatin)), which caused reduced blood cell counts but no tumor regression. He received a second opinion that any further treatment would be in vain, so he opted for an integrative medical approach (via the Integrative Medical Center of New Mexico).

For his non-cancer medical conditions he was given several antacids (Prevacid® 30 mg, Roloids®), antibiotics (Primsol™/Gantan®), antiulcer agents (Mylanta®, Pepto-Bismol®), and the anti-anxiety drug, Xanax®, and then he started an integrative therapy program, the ALA-LDN (Intravenous Alpha-Lipoic Acid- Low-Dose Naltrexone) protocol.

The ALA-LDN protocol comprised alpha-lipoic acid (ALA) (300 to 600 mg intravenously twice weekly), low-dose naltrexone (Vivitrol™)(3 to 4.5 mg at bedtime), and orally, ALA (300 mg twice daily), selenium (200 micrograms twice daily), silymarin (300 mg four times daily), and vitamin B complex (3 high-dose capsules daily). In addition, he maintained a strict dietary regimen, performed a stress-reduction and exercise program, and led a healthy lifestyle. Remarkably, after just one treatment of intravenous ALA his symptoms began to disappear, his quality of life improved, and he had no unwanted side effects.

His pancreatic cancer has remained stable for more than 3-years and he is free from symptoms. Several other patients are being treated with this protocol and, to date, with success (Berkson BM et al 2006). Thus, the ALA-LDN protocol could possibly extend the lives of those pancreatic cancer patients who have been led to believe that their cancer is terminal.

**So How Does It Work?** Alpha-lipoic acid is a potent antioxidant (Baraboi VA 2005), improves immune cells' functions (Mantovani G et al 2000), increases homocysteine levels in cancer cells which is toxic to them (Hultberg B 2003), and prevents the activation of nuclear factor kappaB (NF-kappaB) a key regulator of tumor development and progression (Sokoloski JA et al 1997; Suzuki YJ et al 1992; Vermeulen L et al. 2006). Selenium is useful in elevating antioxidant levels (Woutersen RA et al 1999; Zhan CD et al 2004) and silymarin is a selective COX-2 inhibitor (Cuendet M et al 2000a).

Low-dose naltrexone blocks opiate receptors causing the body to make large amounts of opiates in response, which in turn improve the immune response; specifically, natural killer cell cytotoxicity, B-cell and T-cell proliferation, and IFN-gamma production are maintained during times of immune suppression (Nelson CJ et al 2000).

Prevacid® is an antacid that also improves cell-mediated immunity, prevents immune suppression, and may also exert anti-inflammatory activity, all of which are important for cancer patients with impaired immune systems (Dattilo M et al 1998; Peddicord TE et al 1999).

### ***Innovative Drug Strategies***

Several therapeutic strategies are being explored for the treatment of pancreatic cancer, including:

- Pancreatic enzymes, by prescription, pancrelipase powder, or enteric-coated preparations (Braga M et al 1988; Gonzalez NJ et al 1999; Novak JF et al 2005).
- COX-2 (cyclooxygenase-2) inhibitors, such as Celebrex® (celecoxib) in combination with chemotherapy (Crane CH et al 2003; Ding XZ et al 2000; Lipton A et al 2004; Tseng WW et al 2002; Wei D et al 2004).
- Lipoxygenase inhibitors, such as zileuton, a 5-LOX (5-lipoxygenase) inhibitor.

### ***Pancreatic Enzyme Replacement Therapy***

Dr. John Beard, who published *The Enzyme Theory of Cancer* in 1911, was the first to propose using pancreatic digestive enzymes to treat cancer. Later, Dr. William Donald Kelley treated his cancer patients with enzymes for more than 20 years, and many lived far beyond expectations. By comparison, in a trial of 126 pancreatic cancer patients treated with the drug Gemzar®, not one patient lived longer than 19 months (Burris HA3 1996). Treating patients with pancreatic extract containing enzymes resulted in significantly improved absorption in those with moderate-to-severe fat or protein malabsorption (Perez MM et al 1983).

In a remarkable study by Dr. Nicholas Gonzalez, 11 patients with pancreatic cancer were treated with large doses of pancreatic enzymes, nutritional supplements, "detoxification" procedures, and an organic diet. Of the 11 patients, nine survived for one year, five survived two years, and four survived three years. This pilot study suggests that aggressive nutritional therapy with large doses of pancreatic enzymes significantly increased survival over what would normally be expected for patients with inoperable pancreatic cancer (Gonzalez NJ et al 1999). An experimental animal study found that treating tumors in mice with pancreatic enzyme extract (PPE) significantly prolonged their survival and slowed tumor growth (Saruc M et al 2004).

As a result of the pilot study, the National Cancer Institute and the National Center for Complementary and Alternative Medicine approved funding for a large-scale phase III clinical trial comparing Dr. Gonzalez's nutritional regimen against Gemzar® in treating inoperable pancreatic cancer. This study has full FDA approval and is being conducted under the Department of Surgical Oncology at New York Presbyterian Hospital, Columbia Campus ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)):

- "In the nutritional arm: Patients receive pancreatic enzymes orally every four hours and at meals daily on days 1-16, followed by five days of rest. Patients receive magnesium citrate and Papaya Plus with the pancreatic enzymes. Additionally, patients receive nutritional supplementation with vitamins, minerals, trace elements, and animal glandular products four times per day on days 1-16, followed by five days of rest. Courses repeat every 21 days. Patients consume a moderate vegetarian metabolizer diet during the course of therapy, which excludes red meat, poultry, and white sugar. Coffee enemas are performed twice a day, along with skin brushing daily, skin cleansing once a week with castor oil during the first six months of therapy, and a salt-and-soda bath each week. Patients also undergo a complete liver flush and a clean sweep and purge on a rotating basis each month during the five days of rest."

To learn more about the study and its objectives, call Cara Visser in the office of John Chabot, M.D., Chief of Surgical Oncology at Columbia University, 212-305-0787.

Several factors contribute to the effectiveness of pancreatic enzyme replacement therapy. These include:

- Patient compliance and adherence to scheduled dose and timing of intake.
- Individual weight perception versus actual weight measurement.
- Type of pancreatic enzyme preparations, that is, pancrelipase powder versus enteric-coated products (Schibli S et al 2002). Delayed-release preparations (capsules containing enteric-coated microspheres, such as Creon®) are reportedly less susceptible to acid inactivation in the stomach and duodenum, as they are designed to disintegrate at a relatively high gastrointestinal pH (greater than 5.5 to 6). Antacids or a histamine H2-receptor antagonist (cimetidine, Tagamet®) have been used to decrease the inactivation of enzyme activity.

### ***COX-2 (Cyclooxygenase-2) Inhibitors***

The COX-2 enzyme is elevated in pancreatic cancer (Tucker ON et al 1999) and indirectly prevents cancer cells from dying (Chu J et al 2003). The COX-2 inhibitor Celebrex® reduces levels of the COX-2 enzyme and is now being investigated for use in cancer treatment (Ferrari V et al 2005; Fosslie E 2000; Lipton A et al 2004).

The combination of Celebrex® and 5-FU by prolonged intravenous injection was well tolerated and capable of producing long-lasting, measurable responses, even in patients with advanced pancreatic cancer (Milella M et al 2004). Selective reduction of COX-2 levels improves response to both chemotherapy and radiotherapy without being toxic to normal healthy tissues (Ferrari V et al 2005; Lipton A et al 2004). COX-2 inhibition sensitizes tumor cells to death by radiation and is now being studied in clinical trials (Rich TA et al 2004). However, COX-2 inhibitors may cause heart attack or stroke, as well as kidney damage. Because of these concerns, the FDA-approved drugs Vioxx® and Bextra® have been taken off the market by their manufacturers. Celebrex®, however, is still available.

Suppressing the COX-2 enzyme may inhibit pancreatic cancer cell propagation. In the past, COX-2 inhibitors such as Celebrex® (100-200 mg taken every 12 hours) were considered. However, with recent observations that people taking COX-2 inhibitors for prolonged periods have a higher incidence of cardiac and vascular problems, some of these drugs may no longer be available in the future. Instead, bioflavonoids could be considered at a dose of 250-1800 mg a day, or silymarin (420 mg/day) (Boari C et al 1981; Pares A et al 1998) and/or curcumin (3600 mg/day), which have demonstrated the ability to naturally suppress COX-2 (Gescher A 2004).

### ***5-LOX (5-Lipoxygenase) Inhibitors***

The 5-LOX enzyme is produced in pancreatic cancer (but not in normal pancreatic ducts) and is critical for its growth (Hennig R et al 2002). Reducing levels of 5-LOX prevents human pancreatic cancer cell lines from multiplying and induces apoptosis (cell death). In a phase II study, the 5-LOX inhibitor CV6504 was well tolerated and maintained stable disease. The predicted one-year survival time was approximately 25 percent (Ferry DR et al 2000).

Zileuton, a 5-LOX inhibitor, was approved in the United States in September 2005 for the prevention and chronic treatment of asthma in patients 12 years and older. The drug is contraindicated in patients with active liver disease.

### ***Investigational/Experimental Therapies***

**Oncophage Vaccine.** Antigenics (866-805-8994, [www.antigenics.com](http://www.antigenics.com)) manufactures personalized vaccines or general vaccines, based on the use of heat-shock proteins (BioDrugs et al 2002; Hoos A et al 2003; Oki Y et al 2004).

**GM-CSF Vaccine.** Targets tumor cell lines that produce the immune system-stimulating growth factor known as granulocyte-macrophage colony-stimulating factor (GM-CSF) (Jaffee EM et al 2001; Jaffee EM et al 1998). GM-CSF with synthetic mutant ras peptides resulted in prolonged survival (148 versus 61 days) (Gjertsen MK et al 2001; Gjertsen MK et al 2003).

**Angiogenesis Inhibitors** (tumor-blocker drugs) under testing include PTK787/ZK 222584 (a VEGFR2 inhibitor) (Baker CH et al 2002b; Wiedmann MW et al 2005), VEGF antisense, and TNP-470 (Hotz HG et al 2005; Jia L et al 2005).

**Herceptin® (trastuzumab)** is an antibody that binds to HER2 and may be appropriate for those who have excess HER2 (Safran H et al 2004).

**EGFR-Targeted Therapy:** Produces antibodies against the epidermal growth factor receptor, such as Erbitux™ (cetuximab) or panitumumab (ABX-EGF) (Needle MN 2002; Yang XD et al 2001). In a phase II trial, 41 patients were treated with anti-EGF antibody and Gemzar®. One-year progression-free survival and overall survival rates were 12 percent and 31.7 percent, respectively (Xiong HQ et al 2004a).

## **NUTRITIONAL THERAPY AND SUPPLEMENTS**

Nutritional intervention aims to:

- Reduce the occurrence of pancreatic cancer.
- Decrease treatment-related disease and deaths.
- Enhance response to radiation and chemotherapy.
- Improve long-term survival via direct therapeutic effects.

Consuming a diet rich in fruit and vegetables, plus controlling calories by dietary measures or exercise, will help to prevent

pancreatic cancer (Lowenfels AB et al 2004). A constituent of cruciferous vegetables such as watercress called phenethyl isothiocyanate (PEITC) stopped pancreatic cancer from developing in a hamster model that was given a cancer-causing agent (a carcinogen known as BOP) (Nishikawa A et al 2004).

**Monoterpenes.** Monoterpenes are found in the essential oils of citrus fruits and other plants. The monoterpenes limonene and perillyl alcohol demonstrate intense antitumor activity against pancreatic cancer cells (Crowell PL et al 1996; Gelb MH et al 1995). They counter cancer by:

- Jump-starting enzymes that are able to break down cancer-causing chemicals.
- Preventing cancer cell growth by reducing ras activity and causing cancer cell death.
- Restraining liver enzyme actions (hepatic HMG-CoA reductase activity), which controls cholesterol production and thus cancer cell growth.

**Limonene.** Found in citrus fruits, limonene reduces the growth of pancreatic cancer cells by 50 percent (Karlson J et al 1996). The tentative dose recommendation for limonene is 7.3 to 14.4 grams per day (Boik J 2001; Igimi H et al 1976; Vigushin DM et al 1998). According to studies, limonene is well tolerated in cancer patients at doses that may have clinical activity (Salazar D et al 2002). One partial response in a breast cancer patient at a dose of 8 grams taken twice daily was maintained for 11 months, and three additional patients with colorectal cancer showed disease stabilization for longer than six months on d-limonene at .5 or 1 gram taken twice daily (Vigushin DM et al 1998).

**Perillyl Alcohol.** Perillyl alcohol is found in small concentrations in the essential oils of lavender, peppermint, spearmint, sage, cherries, cranberries, perilla, lemongrass, celery, and caraway seeds (Belanger JT 1998). Perillyl alcohol exhibits powerful effects in minimizing cancer cell growth (Hardcastle IR et al 1999; Stark MJ et al 1995) and preventing the mutated ras proteins from continuously stimulating cancer cell growth (Broitman SA et al 1995; Burke YD et al 2002).

- Twelve clinical trials have investigated the use of perillyl alcohol in various types of cancer treatments. A 2050-mg dose administered four times daily was found to be easily tolerated (Morgan-Meadows S et al 2003). In one clinical trial, perillyl alcohol was administered four times a day to 16 patients with advanced cancers not responding to treatment. Evidence of antitumor activity was seen in a patient with metastatic colorectal cancer who had an ongoing near-complete response of greater than two years' duration. Several patients had stable disease for as long as or greater than six months (Ripple GH et al 2000). The predominant toxicity of perillyl alcohol seen during most trials was gastrointestinal (nausea, vomiting, and belching), limiting the dose. The minimum required antitumor dose is 1.3 grams per day (Boik J 2001).

**Gamma Linolenic Acid (GLA).** GLA, a fatty acid found in borage oil, slows the growth and spread of pancreatic cancer by hindering tumor blood-vessel development (Cai J et al 1999). GLA treatment changes tissue blood flow dramatically in pancreatic tumors, even at low doses (Kairemo KJ et al 1998; Ravichandran D et al 1998).

Intravenous administration of the lithium salt of GLA (Li-GLA) to 48 patients with inoperable pancreatic cancer was associated with longer survival times (Fearon KC et al 1996).

A cell-culture study investigated possible interactions between GLA and 5-FU or Gemzar®. GLA had a synergistic effect with Gemzar® at concentrations that correspond to therapeutic doses in the body. However, GLA with 5-FU was synergistic only within a tight range of high concentrations of 5-FU (Whitehouse PA et al 2003).

**Fish Oil.** Patients with advanced pancreatic cancer usually experience weight loss (catabolic wasting or cachexia) and often fail to gain weight with conventional nutritional support. EPA, an essential fatty acid found in fish oil, restrains pancreatic cancer cell growth in laboratory experiments at low doses and decreases the number of cancer cells at higher doses (Lai PB et al 1996). The maximum tolerated daily dose of fish oil was found to be 0.3 grams per kilogram (kg) of body weight. This means that a 70-kg (154-lb.) patient can generally tolerate up to 21 grams of fish oil containing 13.1 grams of EPA and DHA (Burns CP et al 1999). However, in a phase I study of five pancreatic cancer cachexia patients, a mean dose of approximately 18 grams per day (doses ranged from 9 to 27 grams per day) of a new high-purity preparation of EPA as a 20 percent oil and water diester emulsion was tolerated (Barber MD et al 2001).

Several studies have shown that supplementation with fish oils containing EPA and DHA is helpful and may even reverse weight loss caused by cancer (Merendino N et al 2003; Wigmore SJ et al 2000). Moreover, consumption of a protein- and energy-dense oral nutritional supplement containing omega-3 fatty acids (such as EPA) improves body weight, lean body mass, and quality of life in patients undergoing chemotherapy (Bauer JD et al 2004; Chen da W et al 2005; Klek S et al 2005).

Fish oil supplements providing at least 2400 mg of EPA and 1800 mg of DHA daily have been recommended (Anderson KM et al 1998a). To reduce cachexia, an estimated 2 to 12 grams per day of EPA is needed (Gogos CA et al 1998; Persson C et al 2005; Rosenstein ED et al 2003; Thies F et al 2001).



## ***Clinical Studies: Fish Oil and Pancreatic Cancer***

Many clinical studies have shown that fish oil supplementation stabilizes the rate of weight loss, as well as adipose tissue and muscle mass, in pancreatic cancer patients, who often suffer from wasting (Tisdale MJ 1999).

- Protein supplements enriched with EPA increased total energy expenditure and physical activity levels in advanced pancreatic cancer patients, thereby increasing their quality of life (Klek S et al 2005; Moses AW et al 2004).
- Twenty pancreatic cancer patients were asked to consume two cans of a fish oil-enriched nutritional supplement daily in addition to their normal food intake. Each can contained 16.1 grams of protein and 1.09 grams of EPA. At the study's onset, all patients were losing weight at a median rate of 2.9 kg a month. After administration of the fish oil-enriched supplement, patients had a significant weight gain at both three and seven weeks (Barber MD et al 1999).
- In another study, after three weeks of consuming an EPA-enriched supplement, the body weight of cancer patients had increased, and their energy expenditure in response to feeding had risen significantly to levels no different from baseline healthy control values (Barber MD et al 2000).
- In a study of 18 pancreatic cancer patients who supplemented with fish oil capsules (1 gram each containing EPA 18 percent and DHA 12 percent), patients had a median weight loss of 2.9 kg a month before supplementation; three months after beginning fish oil supplementation, patients had a median weight gain of 0.3 kg a month (Wigmore SJ et al 1996).

## ***Food-Derived Polyphenols***

**Genistein** prevents pancreatic cancer cell growth primarily by regulating sugar metabolism (Boros LG et al 2001). In addition, genistein inactivates NF-kappa B (Li Y et al 2005), thus sensitizing cancer cells to chemotherapeutic agents such as Gemzar® (Banerjee S et al 2005), cisplatin and docetaxel (Li Y et al 2004), and VP-16 and doxorubicin (Sato T et al 2003). In laboratory experiments, genistein has been shown to improve survival, reduce tumor blood-vessel development (Buchler P et al 2004), almost completely inhibit cancer metastasis, and increase cancer cell suicide (Buchler P et al 2003).

If the pathology report shows that the pancreatic cancer cells have a mutated p53 oncogene, or if there is no p53 detected, then high-dose genistein therapy may be appropriate (Choi YH et al 2000; Wilson LC et al 2003). If the pathology report shows a functional p53, then genistein is less effective in stopping cancer growth. The suggested dose of genistein is approximately 500 mg daily (Miltyk W et al 2003; Takimoto CH et al 2003).

**Green Tea.** Tea is particularly rich in polyphenols such as epigallocatechin gallate (EGCG) that act as antioxidants. Black and green tea extracts reduce pancreatic tumor cell growth by approximately 90 percent while preventing angiogenesis (Maiti TK et al 2003; Masamune A et al 2005; Roomi MW et al 2005). They also decrease the expression of the K-ras gene (Lyn-Cook BD et al 1999a) and the invasiveness of pancreatic cancer cells (Takada M et al 2002). Animal experiments of pancreatic cancer show that tea polyphenols restrain carcinogen-induced increases in oxidative DNA damage (Frei B et al 2003).

Green tea extract curbs the process of pancreatic cancer development (Lyn-Cook BD et al 1999b) and the promotion of transplanted human pancreatic cancer in animals, and also causes pancreatic cancer cell death (Hiura A et al 1997; Qanungo S et al 2005).

In humans, an inverse relationship was observed between the amount of green tea consumed and the risk of developing pancreatic cancer; the highest intake was associated with the lowest risk of cancer (Ji BT et al 1997). In clinical studies, green tea supplementation has been shown to be safe and protective (Ahn WS et al 2003; Chow HH et al 2001; Chow HH et al 2003).

**Antioxidants.** Free radicals can cause repeated damage to normal cells and reduce the function of injured tissues. When sufficient antioxidants are available, free radicals are removed before excess damage occurs. Antioxidant levels are reduced in pancreatic cancer compared to other pancreatic diseases and healthy pancreatic tissue, resulting in increases in reactive oxygen (Cullen JJ et al 2003) that are capable of stimulating cancer cell division (Garcea G et al 2005; Vaquero EC et al 2004).

Increased levels of some antioxidants may be useful in slowing the growth of pancreatic cancer (Weydert C et al 2003). Vitamins A, C, and E, as well as selenium, increase antioxidants in the body needed to reduce free-radical damage (Woutersen RA et al 1999).

**Vitamins A, C, and E.** In animals in which pancreatic cancer was caused by chemicals, cancer incidence was decreased by 64.3 percent by vitamin A and by 71.4 percent with vitamin C. Both vitamins increased SOD (superoxide dismutase) activity and were toxic to tumor cells but not to normal healthy cells (Wenger FA et al 2001).

- An overview of 14 randomized trials (with a total of 170,525 patients) showed significant effects of supplementation with beta-carotene, vitamins A, C, E, and selenium (alone or in combination) versus placebo on pancreatic cancer incidence (Bjelakovic G et al 2004).
- A study of 23 pancreatic cancer patients tested retinol palmitate (vitamin A) and beta-interferon with chemotherapy. Eight

patients responded and eight patients had stable disease. For all patients, median time to disease progression and survival time were 6.1 months and 11 months, respectively. Toxicity was high, but patients who had responses and disease stabilization had prolonged symptom relief (Recchia F et al 1998).

- Retinoids curb the growth and adhesion of a variety of pancreatic cancer types, even those that previously have been documented to be resistant to retinoids (El-Metwally TH et al 1999). Vitamin E succinate restrained pancreatic cancer cell growth in laboratory experiments (Heisler T et al 2000).
- Ascorbyl stearate, a fat-soluble form of ascorbic acid (vitamin C), markedly restrained the growth of—and even killed—pancreatic cancer cells (Naidu KA et al 2003).

**Selenium.** Selenium and beta-carotene were found to restrain the growth of pancreatic tumors caused by carcinogen exposure in mice (Appel MJ et al 1996). Selenium levels were found to be reduced in pancreatic cancer patients who underwent surgery to remove the upper portion of their intestine (Armstrong T et al 2002). In preclinical studies, a diet high in selenium reduced the number of carcinogen-induced pancreatic cancers significantly (Kise Y et al 1990).

**Curcumin** has many anticancer effects. It is a selective inhibitor of the COX-2 enzyme and may be beneficial in preventing and treating pancreatic cancer (Cuendet M et al 2000). It decreases NF-kappa B activity, which is involved in controlling the growth of pancreatic cancer cells (Li L et al 2004). It also inhibits interleukin-8 (IL-8) production, which affects invasiveness, cell growth, and tumor blood-vessel development (Hidaka H et al 2002).

## COMPLEMENTARY ALTERNATIVE THERAPIES

**PSK (Polysaccharide K).** PSK is a protein-bound polysaccharide derived from the mycelium of the mushroom *Coriolus versicolor* (Tsukagoshi S et al 1984). In Japan, PSK is used as a non-specific biological response modifier to enhance the immune system in cancer patients (Koda K et al 2003; Noguchi K et al 1995; Yokoe T et al 1997). PSK suppresses tumor cell invasiveness by down-regulating several invasion-related factors (Zhang H et al 2000). Also, PSK can enhance pancreatic cancer cell death induced by Taxotere® (docetaxel) (Zhang H et al 2003).

Two patients who had unresectable pancreatic cancer were treated with combined chemotherapy using cisplatin, PSK, and UFT (uracil-tegafur). During therapy, a partial response was observed, with a remarkable decrease in tumor size and no significant side effects. From the results of these two cases, this combination chemotherapy was considered to be one of the most effective therapies available for pancreatic cancer (Sohma M et al 1987). PSK has been used as adjuvant immunotherapy for cancer at a dose of 3 grams daily (Ito K et al 2004; Ohwada S et al 2004; Toge T et al 2000).

**Ukrain (NSC-631570).** Ukrain, a semisynthetic agent, has been used in complementary medicine for more than 20 years to treat benign and malignant tumors. In a phase II trial of advanced pancreatic cancer patients, Ukrain either alone or together with Gemzar® (gemcitabine) was found to be well-tolerated with only moderate toxicity, and doubled median survival times (Gansauge F et al 2002). In another study, Ukrain improved the quality of life of patients suffering from advanced pancreatic cancer while significantly prolonging their survival time (Zemskov V et al 2002).

### ***For More Information***

Pancreatic cancer is usually associated with weight loss (catabolic wasting) and pain. The following protocols may be useful in designing a program that will address specific needs:

- Catabolic Wasting
- Pain
- Cancer Surgery
- Complementary Adjuvant Therapies
- Cancer Chemotherapy
- Cancer Radiation
- Diabetes

## LIFE EXTENSION FOUNDATION RECOMMENDATIONS

Pancreatic cancer is a rapidly progressive disease with generally poor survival time. The goal of therapy is to strengthen pancreatic function, impede cancer growth and spread, and reduce the severity of symptoms. Various nutritional supplements outlined in this chapter have been shown to help pancreatic cancer patients by slowing disease progression or increasing quality of life.

### ***Guidelines for Reducing Pancreatic Cancer Risk***

1. Stop smoking and drinking alcohol.
2. Avoid or reduce exposure to toxic chemicals and petroleum products.
3. Maintain a healthy body weight.
4. Reduce dietary intake of fried foods, red meat, and meat products.
5. Increase intake of fresh fruit and vegetables, fiber, minerals, and vitamins.
6. Reduce sugar consumption (glycemic load).
7. Increase physical activity.
8. Maintain a diet suitable for diabetics that restricts simple carbohydrates such as sugar and emphasizes complex carbohydrates (fibers) and proteins (refer to the Diabetes protocol). Protein supplements such as soy and essential fatty acids such as borage and fish oils will help by altering the dietary intake ratio of carbohydrates, proteins, and fats.

If pancreatic cancer patients are to improve their odds of achieving a remission or long-term survival, they should attempt to integrate into their conventional therapy as many of the following dietary changes and supplements as possible, but only under a physician's supervision.

- **Aged Garlic Extract**—1200 milligram (mg) daily
- **Alpha-tocopherol**—400 international units (IU) daily
- **Ascorbic acid**—500 to 3000 mg daily
- **Beta-carotene**—20 mg daily
- **Curcumin**—2400 mg daily, two hours apart from medications
- **d-Limonene**—7.3 to 14.4 grams (g) daily
- **Fiber**—4 to 12 g daily before meals
- **Fish oil concentrate**—700 to 4200 mg of EPA, 500 to 2000 mg of DHA daily
- **Life Extension Booster**—1 capsule daily
- **Gamma-linolenic acid (GLA)**—700 to 900 mg daily
- **Grape seed extract**—100 mg daily
- **Green tea extract (EGCG)**—800 mg daily
- **Life Extension Mix multivitamin/multi-mineral formula without copper**—follow label directions
- **Lycopene**—15 to 30 mg daily
- **Perillyl alcohol**—2050 mg, four times daily
- **PSK (Coriolus versicolor)**—3 grams daily
- **Selenium**—600 micrograms (mcg) daily
- **Silymarin**—100 to 420 mg daily
- **Soy extract (genistein)**—656 mg daily
- **Vitamin A**—10,000 IU daily
- **Zinc**—45 to 50 mg daily.

### ***Innovative Drug Strategies***

The following should be used only under a physician's supervision:

- Pancreatic enzymes (by prescription)—1000 to 10,000 U lipase per kg of body weight per meal (Schibli S et al 2002). Delayed-release preparations (capsules containing enteric-coated microspheres, such as Creon®) are reportedly less susceptible to acid inactivation.
- Antacids or a histamine H2-receptor antagonist (cimetidine, Tagamet®) have been used to decrease the inactivation of pancreatic enzyme activity.
- Celebrex® (celecoxib)—400 mg twice daily.
- Zylflo® (zileuton)—400 to 800 mg twice daily (except for those with active liver disease).
- Ukrain (NSC-631570). Ukrain is supplied as a solution ready for injection. A Ukrain therapy cycle consists of 10 mg taken intravenously every other day for 20 days. A vitamin C cycle is added to the Ukrain cycle, 3 grams taken intravenously every other day, and 2.4 grams taken orally in three divided doses on the same days, for 20 days (Zemskov V et al 2002).

### **PRODUCT AVAILABILITY**

All the nutrients and supplements discussed in this section are available through the Life Extension Foundation Buyers Club, Inc. For ordering information, call anytime toll-free 1-800-544-4440, or visit us online at [www.LifeExtension.com](http://www.LifeExtension.com).

## ***Pancreatic Cancer Safety Caveats***

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

### **Beta-Carotene**

- Do not take beta-carotene if you smoke. Daily intake of 20 milligrams or more has been associated with a higher incidence of lung cancer in smokers.
- Taking 30 milligrams or more daily for prolonged periods can cause carotenoderma, a yellowish skin discoloration (carotenoderma can be distinguished from jaundice because the whites of the eyes are not discolored in carotenoderma).

### **Curcumin**

- Do not take curcumin if you have a bile duct obstruction or a history of gallstones. Taking curcumin can stimulate bile production.
- Consult your doctor before taking curcumin if you have gastroesophageal reflux disease (GERD) or a history of peptic ulcer disease.
- Consult your doctor before taking curcumin if you take warfarin or antiplatelet drugs. Curcumin can have antithrombotic activity.
- Always take curcumin with food. Curcumin may cause gastric irritation, ulceration, gastritis, and peptic ulcer disease if taken on an empty stomach.
- Curcumin can cause gastrointestinal symptoms such as nausea and diarrhea.

### **EPA/DHA**

- Consult your doctor before taking EPA/DHA if you take warfarin (Coumadin). Taking EPA/DHA with warfarin may increase the risk of bleeding.
- Discontinue using EPA/DHA 2 weeks before any surgical procedure.

### **Fiber**

- Take fiber supplements with a full 8-ounce glass of water.
- Drink eight 8-ounce glasses of water daily while taking fiber.

### **Garlic**

- Garlic has blood-thinning, anticlotting properties.
- Discontinue using garlic before any surgical procedure.
- Garlic can cause headache, muscle pain, fatigue, vertigo, watery eyes, asthma, and gastrointestinal symptoms such as nausea and diarrhea.
- Ingesting large amounts of garlic can cause bad breath and body odor.

### **Genistein**

- Consult your doctor before taking genistein/genistin if you have prostate cancer.
- Do not take genistein/genistin if you have estrogen receptor-positive tumors.
- Genistein/genistin can cause hypothyroidism in some people.

### **GLA**

- Consult your doctor before taking GLA if you take warfarin (Coumadin). Taking GLA with warfarin may increase the risk of bleeding.
- Discontinue using GLA 2 weeks before any surgical procedure.
- GLA can cause gastrointestinal symptoms such as nausea and diarrhea.

## Green Tea

- Consult your doctor before taking green tea extract if you take aspirin or warfarin (Coumadin). Taking green tea extract and aspirin or warfarin can increase the risk of bleeding.
- Discontinue using green tea extract 2 weeks before any surgical procedure. Green tea extract may decrease platelet aggregation.
- Green tea extract contains caffeine, which may produce a variety of symptoms including restlessness, nausea, headache, muscle tension, sleep disturbances, and rapid heartbeat.

## Selenium

- High doses of selenium (1000 micrograms or more daily) for prolonged periods may cause adverse reactions.
- High doses of selenium taken for prolonged periods may cause chronic selenium poisoning. Symptoms include loss of hair and nails or brittle hair and nails.
- Selenium can cause rash, breath that smells like garlic, fatigue, irritability, and nausea and vomiting.

## Vitamin A

- Do not take vitamin A if you have hypervitaminosis A.
- Do not take vitamin A if you take retinoids or retinoid analogues (such as acitretin, all-trans-retinoic acid, bexarotene, etretinate, and isotretinoin). Vitamin A can add to the toxicity of these drugs.
- Do not take large amounts of vitamin A. Taking large amounts of vitamin A may cause acute or chronic toxicity. Early signs and symptoms of chronic toxicity include dry, rough skin; cracked lips; sparse, coarse hair; and loss of hair from the eyebrows. Later signs and symptoms of toxicity include irritability, headache, pseudotumor cerebri (benign intracranial hypertension), elevated serum liver enzymes, reversible noncirrhotic portal high blood pressure, fibrosis and cirrhosis of the liver, and death from liver failure.

## Vitamin C

- Do not take vitamin C if you have a history of kidney stones or of kidney insufficiency (defined as having a serum creatine level greater than 2 milligrams per deciliter and/or a creatinine clearance less than 30 milliliters per minute).
- Consult your doctor before taking large amounts of vitamin C if you have hemochromatosis, thalassemia, sideroblastic anemia, sickle cell anemia, or erythrocyte glucose-6-phosphate dehydrogenase (G6PD) deficiency. You can experience iron overload if you have one of these conditions and use large amounts of vitamin C.

## Zinc

- High doses of zinc (above 30 milligrams daily) can cause adverse reactions.
- Zinc can cause a metallic taste, headache, drowsiness, and gastrointestinal symptoms such as nausea and diarrhea.
- High doses of zinc can lead to copper deficiency and hypochromic microcytic anemia secondary to zinc-induced copper deficiency.
- High doses of zinc may suppress the immune system. High doses of zinc may be immunosuppressive.

For more information see the Safety Appendix

## PSK SOURCES

A PSK/Japanese formula called VPS® Coriolus versicolor is available from JHS Natural Products and can be ordered online (<http://www.jhsnp.com>) or by calling 1-888-330-4691 (toll-free in the U.S. only) or 1-541-344-1396 for international callers.

Each capsule of VPS® Coriolus versicolor extract contains 625 mg, requiring five capsules daily to equal the 3-gram dosage. The manufacturer recommends that the daily dose be split between morning and evening, taking three capsules in the morning and two capsules in the evening, as close to 12 hours apart as possible, preferably on an empty stomach or with a light meal.

## DRUG AVAILABILITY

For information on how to obtain Ukrain, please contact:  
Ukrainian Anticancer Institute  
Velyka Zhytomyrska 17/28,

Kiev, Ukraine  
Tel: (+380) 44 27237191  
Fax: (+380) 44 2723791

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