

# Pancreatic Cancer

By Ronald Steriti, NMD, PhD

## Overview

Pancreatic cancer is the fifth leading cause of cancer mortality in the United States. The American Cancer Society (ACS) estimates that 29,000 Americans died from pancreatic cancer in 1998. Conventional medicine's inability to effectively treat pancreatic cancer is evidenced by survival rates of only 18% at 1 year and 4% at 5 years - one of the poorest 5-year survival rates of any cancer. The tumor results in the death of more than 98% of afflicted patients.

The pancreas can be divided into two basic parts, the exocrine and endocrine pancreas. Each has a different function. The exocrine pancreas produces juices (pancreatic enzymes) that help break down and digest food. The endocrine pancreas produces hormones (such as insulin) that regulate how the body stores and uses food. About 95% of pancreatic cancers begin in the exocrine pancreas. The rest are cancers of the endocrine pancreas, which are also called islet cell cancers.

## Causes

Several factors have been reported to increase the incidence of pancreatic cancer:

- Smoking is the most consistently observed risk factor. Heavy smokers are two to three times more at risk for the disease than nonsmokers.
- Occupational exposure to gasoline, organic solvents (naphthalene, 2-naphthylamine or benzidine), or petroleum products is associated with an increased risk
- Elderly, heavy-smoking alcoholic men exposed to occupational carcinogens have an especially high risk.
- Long-standing chronic pancreatitis or diabetes mellitus.
- Diets high in total or animal fats.
- Coffee and alcohol consumption was considered a risk factor at one time, but recent studies do not support this.
- DDT exposure. (Garabrant, Held et al. 1992)

## Nutritional Influences

A review of epidemiological evidence on the relationship between nutrition and pancreatic cancer found that, overall, fairly consistent patterns of positive associations with the intake of meat, carbohydrates, and dietary cholesterol have been observed. Consistent inverse relationships with fruit and vegetable intakes and, in particular, with fiber and vitamin C, have also been noted. (Ghadirian, Thouez et al. 1991; Ji, Chow et al. 1995; Howe and Burch 1996)

An article translated from the Japanese journal *Gan No Rinsho* compared 71 patients with pancreatic cancer to 142 community-based controls. They found significantly decreased risks were associated with consumption of raw vegetables and green tea. The risk increased

significantly with consumption of the fat of meat, boiled fish, coffee, black tea and alcoholic beverages. (Goto, Masuoka et al. 1990)

#### PHYTOESTROGENS

A recent paper published in the Australian journal *Surgery* presented evidence to support the hypothesis that the increased incidence of pancreatic cancer in Western communities may be related to the relatively low dietary content and protective qualities of naturally occurring plant hormones (phytoestrogens) and related compounds. (Stephens 1999)

#### FOLATE

An article published in the American journal *Epidemiology* described a cohort study of 27,101 healthy male smokers aged 50 to 69 years. 157 of them developed pancreatic cancer during the 13 years of follow-up from 1985 to 1997. The adjusted hazards ratio comparing the highest with the lowest quintile of dietary folate intake was 0.52 (95% confidence interval: 0.31, 0.87; p-trend = 0.05). Dietary methionine, alcohol intake, and smoking history did not modify this relation. Consistent with prior studies, this study shows that cigarette smoking was associated with an increased risk. The authors conclude that these results support the hypothesis that dietary folate intake is inversely associated with the risk of pancreatic cancer and confirm the risk associated with greater cigarette smoking. (Stolzenberg-Solomon, Pietinen et al. 2001)

#### LYCOPENE

An article presented in the *American Journal of Clinical Nutrition* described a study of serum collected from 25,802 volunteers which showed that low levels of serum lycopene were strongly associated with pancreatic cancer and less strongly associated with cancer of the bladder and rectum. (Comstock, Helzlsouer et al. 1991)

An earlier study also published in the *American Journal of Clinical Nutrition* found that serum levels of lycopene and selenium were lower in patients who had pancreatic cancer than in matched controls. The authors concluded that the serum levels of selenium were significant but its effect was seen principally in men. (Burney, Comstock et al. 1989)

One study found that rats given a diet high in beta-carotene, vitamin C or selenium, but not vitamin E, developed fewer pancreatic tumors induced artificially in mice than controls. (Woutersen, Appel et al. 1999)

#### OLIVE OIL

In a study of 362 pancreatic cancer cases and 1502 controls in Italy, olive oil was found to have a comparatively more favorable impact on the risk of pancreatic cancer than other types of seasoning fats. (La Vecchia and Negri 1997)

#### **Genetic Damage**

Genetic damage is highly associated with pancreatic cancer. Several genes have been associated with pancreatic cancer, including:

- The Kirsten-Ras gene
- The p16 gene
- The p53 gene
- The FHIT gene

## RAS GENES

Over 85% of pancreatic cancer patients have mutations in Kirsten-Ras genes, almost always on codon 12. The family of Ras proteins plays a central role in the regulation of cell growth and integration of regulatory signals that govern the life cycle of the cell and cellular proliferation. Mutations in the Ras genes result in the transformation of normal cells into cancerous cells that grow rapidly and form tumors. Mutation of the Ras gene is the single most common genetic abnormality in human tumors.

## P16 GENE

The development of pancreatic cancer has been associated with a mutation of the *p16<sup>INK4</sup>* gene located on chromosome 9p21, a gene also implicated in the pathogenesis of cutaneous malignant melanoma (skin cancer).

## P53 GENE

Mutations in the tumor-suppressor gene p53 have been associated with pancreatic cancer. Since p53 is a repair gene, when it malfunctions, damaged DNA is able to proliferate and form cancerous cells. (Berrozpe, Schaeffer et al. 1994)

## FHIT GENE

A recent article published in the *Proceedings of the National Academy of Sciences* discussed the findings of scientists from Jefferson Medical College in Philadelphia who investigated tumor suppressor gene FHIT in mice. The FHIT gene induces apoptosis (cell death) and slows proliferation of tumor cells. The gene exists at a fragile site on chromosome 3p14 and is easily damaged by environmental carcinogens. It has been found to be deleted in many types of cancer, including breast, lung, esophageal, pancreatic, gastric and head and neck cancers. (Mangray and King 1998; Simon, Bartsch et al. 1998; Sorio, Baron et al. 1999; Hilgers, Koerkamp et al. 2000)

## **Labs**

The early diagnosis of pancreatic cancer is difficult, even with recent advances in diagnostic methods. The symptoms are insidious (developing gradually and steadily) and are often present for two months before the diagnosis is made. The delay in making an appropriate diagnosis is due to the poor sensitivity and high false negative rates of the techniques.

## BLOOD TESTS

The CA 19-9 cancer tumor marker is ordered when pancreatic cancer is suspected in a patient with jaundice (yellowing of the skin due to liver malfunction). Further diagnostic methods are required as it is only 70% sensitive and 87% specific for pancreatic cancer.

## IMAGING

Ultrasound scans are usually ordered during the jaundice work-up. Normal ultrasounds have a 36% false negative rate for pancreatic cancer.

A CT scan of the abdomen usually detects the presence of a pancreatic mass, although it has a 25% false negative rate. Sometimes only generalized pancreatic enlargement is seen which suggests chronic pancreatitis instead of pancreatic cancer.

Endoscopic retrograde cholangiopancreatography (ERCP) is often helpful to clarify ambiguous CT or ultrasound findings. In this test, dye is injected through a tube that is fed orally down to the stomach, into the small intestines, and inserted into the drainage duct of the pancreas. ERCP has a false negative rate of only 5% for pancreatic cancer.

Percutaneous transhepatic cholangiography (PTC) can also help find cancer of the pancreas. During this test, a thin needle is inserted into the liver and dye is injected into the bile ducts so that blockages can be seen on X-rays. A fine tube is sometimes left in the right side of the liver to drain excess bile and relieve jaundice.

## PATHOLOGY

Needle aspiration cytology is 60-90% sensitive and is often ordered during ERCP and PTC procedures to be absolutely certain that cancer exists. Unfortunately it can cause metastasis (seeding of the cancer to other sites).

## Conventional Treatment

### ***Surgery***

Some cases (10-15%) are eligible for complete surgical removal of the tumor (a Whipple resection). It is, however, a high-risk procedure with a mortality rate of 15% and a five-year survival rate of only 10%. The median survival time for non-operable cases (the majority) is only 6 months. Management of these cases is based on relieving symptoms.

Chemotherapy with 5-fluorouracil (5-FU) and radiation have been used in combination after pancreatic surgery. One study of patients that had undergone a Whipple resection showed that radiation combined with 5-fluorouracil showed an average improvement in survival time from 11 to 20 months.

### ***Radiation***

Radiation therapy alone can improve pain and may prolong survival. The results are dose-related and precision external-beam techniques are required.

### ***Pain Management***

Patients can be given slow-release morphine orally, intravenously, or by epidural infusion using a portable pump. Side effects of morphine include constipation, nausea and drowsiness. NSAIDs are to be used with extreme care in pancreatic cancer as they may precipitate acute renal failure.

## **Chemotherapy**

While many drugs have been evaluated, no single chemotherapy drug has produced more than a 15% response rate or median survival greater than 3 months.

### **5-FLUOROURACIL**

Chemotherapy with 5-fluorouracil (5-FU) is associated with a response rate of less than 20% and does not improve the survival rate. As a result of these disappointing findings, multiple drug therapies have been used without much greater success.

A German study evaluated 5-fluorouracil (5-FU) combined with ginkgo biloba extract in 32 individuals with advanced pancreatic cancer. Progressive disease was observed in 22 (68.8 %), no change in 7 (21.9 %), and partial response in 3 (9.4 %). The overall response was 9.4%. In comparison with the results of the studies with the drug gemcitabine hydrochloride, the combination of 5-FU and ginkgo biloba extract shows comparable response rates with a low toxicity. The results suggest a good benefit-risk ratio for the combination of 5-FU and ginkgo biloba extract in the treatment of pancreatic cancer. (Hauns, Haring et al. 1999)

In Europe, oncologists are combining 5-FU with borage oil (gamma-linolenic acid) to improve absorption of 5-FU. (Umejima, Kikuchi et al. 1995)

### **ACCUTANE**

Based on the need to inhibit pancreatic cancer cell division at different stages of its growth and induce apoptosis (programmed cell death) of cancer cells, multiple therapeutic modalities are often recommended. One successful treatment modality is to combine the differentiating-inducing drug Accutane (13-cis-retinoic acid) with other chemotherapy drugs, such as 5-fluorouracil (5-FU). Both Accutane and 5-FU are toxic drugs that must be carefully administered by a medical oncologist.

In an article published in the journal *Cancer*, a combination of 13-cis-retinoic acid (Accutane) and interferon-alpha were tested in a phase II trial of 22 patients with pancreatic cancer. One patient experienced partial remission and fourteen patients demonstrated stable disease for about 5 months. (Brembeck, Schoppmeyer et al. 1998)

### **GEMCITABINE**

A new drug by injection, Gemcitabine hydrochloride (Gemzar), has shown moderate promise. Gemcitabine inhibits the enzyme responsible for DNA synthesis.

A review article published in the journal *Oncology* discussed Gemcitabine and in comparison to 5-fluorouracil. Treatment with the single-agent Gemcitabine achieved clinical benefit in 20-30% of patients. The one-year survival rate of Gemcitabine is 18% compared with a 2% rate for 5-fluorouracil. (Heinemann 2001)

Recent studies show a modest improvement by combining gemcitabine with 5-fluorouracil or cisplatin. (Brodowicz, Wolfram et al. 2000; Oettle, Arning et al. 2000)

For gemcitabine to work effectively, the cancer cells should have a mutant K-Ras oncogene present. Over 85% of pancreatic cancers express a mutated K-Ras oncogene.(Kijima and Scanlon 2000)

#### IFOSFAMIDE

In a study reported in the journal *Clinical Oncology*, 29 patients with pancreatic cancer were treated by injection with Ifosfamide, a chemotherapy drug approved for use in a wide variety of other cancers. In addition to Ifosfamide, N-acetylcysteine (NAC) was administered as a protective agent. Nausea and vomiting occurred in the majority of the treated patients. Other adverse effects noted were mild myelo-suppression, CNS toxicity, and one case of acute renal failure. One complete response and five partial responses were observed in 27 patients. (Loehrer, Williams et al. 1985; Einhorn and Loehrer 1986)

#### PACLITAXEL

Paclitaxel (Taxol) is a drug extracted from the needles of the European yew *Taxus baccata* that inhibits microtubule syntheses, an essential part of cell division and growth.

Taxol was shown to inhibit growth in human pancreatic adenocarcinoma cell lines with mutant p53 genes. (Gururajanna, Al-Katib et al. 1999)

Another study combined Taxol with Tiazofurin and showed that the combination had a synergistic effect in human ovarian, pancreatic, and lung carcinoma cell lines. (Taniki, Prajda et al. 1993)

#### DOCETAXEL

Docetaxel (Taxotere) is a chemical synthesized from *Taxus baccata* that retains the unique mechanism of action of Taxol and inhibits the depolymerization of microtubules into tubulin. Based on the results of Phase II clinical trials, Docetaxel is currently approved for use in breast and lung cancer.

Taxotere was shown to be active with 80% complete regressions against advanced C38 colon adenocarcinoma and PO3 pancreatic ductal adenocarcinoma. (Lavelle, Gueritte-Voegelein et al. 1993)

A recent article published in the European journal *Cancer*, described a Phase II study of 40 patients with pancreatic cancer that were treated with Docetaxel. Six patients (15%) experienced a partial response. Stable disease was recorded in 15 patients (38%). The median duration of response was 5.1 months, with a range of 3.1-7.2 months.(Rougier, Adenis et al. 2000)

Docetaxel and Gemcitabine were used in combination to treat fifteen patients with pancreatic cancer. Four patients (27%) achieved an objective response by CT scan, including one complete response. Seven patients (47%) had subjective improvement and decreased serum marker levels of CA 19-9. In vitro testing showed that Docetaxel and Gemcitabine were minimally effective alone but when combined, they displayed additional anti-proliferative effects.(Sherman and Fine 2001)

A second study of fifty-four patients treated with Docetaxel and Gemcitabine had similar results. Seven patients (13%) achieved partial response and 18 (33%) stable disease. The median duration of response was 24 weeks, time to tumor progression 32 weeks, and overall survival 26 weeks. (Stathopoulos, Mavroudis et al. 2001)

In a recent trial, Docetaxel used to treat twenty-one Japanese patients with pancreatic cancer did not show promising results. None of the patients achieved an objective response; seven showed no change and 13 showed progressive disease. In one patient, the response was not assessable because of early death. The median survival time for all patients was 118 days. (Okada, Sakata et al. 1999)

## TRIMETREXATE

Trimetrexate (Neutrexin) is a folate antagonist structurally similar to methotrexate and trimethoprim. Trimetrexate was approved by the FDA in 1993 for use in colorectal and pancreatic cancer, and *Pneumocystis carinii* pneumonia. Trimetrexate inhibits the enzyme dihydrofolate reductase which converts dihydrofolate into the biologically active tetrahydrofolate, which is needed for the synthesis of purines, DNA and cellular proteins.

## CAFFEINE

Caffeine, even though it is associated with increased risk of developing pancreatic cancer, has been studied for use in combination with other chemotherapy drugs. Unfortunately the results were not very promising, but the research provides an interesting viewpoint on the conventional philosophy underlying chemotherapy.

An article published in the American Journal *Clinical Oncology* describes a phase II study using cisplatin, cytarabine, and caffeine with a continuous intravenous infusion of 5-fluorouracil (5-FU) for the treatment of pancreatic carcinoma. Thirty eligible patients were entered in the study. A complete remission was seen in 2 patients and partial remission in 3 patients, for an overall response rate of 16.7%. The median survival was 5.0 months (range: 0.3-32.4 months) and 16.7% and 10% of patients were alive at 1 and 2 years. Although the combination chemotherapy treatment produced durable responses in pancreatic cancer, the toxicity was substantial. (Ahmed, Vaitkevicius et al. 2000)

A study published in the journal *Cancer* describes two clinical trials of caffeine used to treat patients with advanced pancreatic cancer. In a Phase I clinical trial, seven of 18 patients with measurable disease had partial responses to caffeine. A subsequent Phase III clinical trial compared caffeine versus standard treatment using streptozotocin, mitomycin, and 5-fluorouracil (referred to as SMF). Two patients (5.5%) on caffeine treatment and four patients (10.2%) on the SMF treatment had objective responses (partial response or improvement). No complete remissions were observed. The median duration of survival for all patients on the SMF treatment protocol was 10 months, although it was 5 months on the caffeine treatment. The authors of the study concluded that neither regimen is effective treatment for advanced pancreatic cancer. (Kelsen, Hudis et al. 1991)

In a phase I-II study, 28 patients with advanced pancreatic adenocarcinoma were treated with cisplatin, high-dose cytarabine (ARA-C), and caffeine. Eighteen of the 28 patients had measurable or assessable disease; seven (39%) had partial responses. The median response

duration was 6.2 months. Median survival for responders was 9.5 months with two patients surviving for more than 18 months. Median survival for all patients was 6.1 months. (Dougherty, Kelsen et al. 1989)

In an article published in the journal *Carcinogenesis*, caffeine was injected into male Wistar rats that had been injected with the tumor-forming drug 4-hydroxyaminoquinoline 1-oxide (4-HAQO). The caffeine was used to impeded DNA synthesis. A dose-dependant relationship was observed with the higher dose decreasing the total number of nodules, and the lower dose increasing the number of nodules. (Denda, Yokose et al. 1983)

## **New Drug Research**

At the time this article was written, about fifty clinical trials for pancreatic cancer were actively underway. For a list of these trials, visit the Cancer Option web site at

[www.CancerOption.com](http://www.CancerOption.com)

### ***Camptothecin***

Camptothecin is derived from the wood and bark of the Chinese tree *Camptotheca acuminata*, the so-called “happy tree.” The active ingredient was discovered in 1966 by the same researchers that isolated Taxol. In 1985 it was discovered that camptothecin inhibited the enzyme DNA topoisomerase which is extremely important in cell replication and DNA transcription and recombination. There are several camptothecin-derived drugs, including Topotecan from SmithKline Beecham, CPT-11 from Diichi in Japan, GG211 by Glaxo, and 9-nitrocamptothecin (Rubitecan) from SuperGen. (Moss 1998)

### **RUBITECAN**

A study appearing in the May 1999 issue of the *International Journal of Oncology* reported on a group of end-stage pancreatic cancer patients treated with an experimental drug called Rubitecan (also known as 9-nitrocamptothecin and RFS-2000). The patients had failed all previous conventional therapies and were thus eligible to participate in this clinical study. Of the 60 patients who were able to complete the therapy, 31.7% responded favorably with a median survival of 18.6 months. Another 31.7% were stabilized with a 9.7 month median survival rate, while 36.6% were non-responders with a 6.8 month median survival rate. (Stehlin, Giovanella et al. 1999)

Phase III clinical trials of Rubitecan began in 1999 and enrollment was completed in February, 2001 with more than 400 patients that had previously tried Gemzar (Gemcitabine) without success. Each patient was then randomized to either Rubitecan or 5-FU. SuperGen is currently analyzing the data from this clinical trial and has begun the laborious process of compiling a New Drug Application (NDA), which they plan to submit in the latter half of 2001. Several clinical trials using Rubitecan in combination with other chemotherapy drugs are still underway. One study is using Rubitecan for pancreatic patients that have not undergone chemotherapy. For more information, contact SuperGen at:

SuperGen  
Phone (925) 560-0100  
[www.supergen.com](http://www.supergen.com)

## **Oncophage**

An experimental pancreatic cancer vaccine is being tested by Antigenics. The vaccine is based on technology that uses heat shock proteins (HSPs). HSPs are naturally formed when a cell is stressed by things such as heat, cold, or glucose or oxygen deprivation. Most tumors release a constant flow of necrotic (dead) cells, exposing their HSPs, which are bound to peptides, to the immune system. The HSP-peptide complex stimulates precisely targeted cytotoxic T-cells and non-specific natural killer (NK) cells. Antigenics makes personalized vaccines from the cells of surgically removed tumors.

Antigenics

Phone: (866) 805-8994

[www.antigenics.com](http://www.antigenics.com)

## **GM-CSF Vaccine**

The GM-CSF vaccine consists of tumor cell lines that are genetically engineered to produce the immune system-stimulating cytokine known as granulocyte-macrophage colony-stimulating factor (GM-CSF). The immune system would be able to recognize the pancreatic cancer cells as foreign and mount an attack against them.

A study conducted at Johns Hopkins University published in the January 2001 issue of the *Journal of Clinical Oncology* revealed the results of the GM-CSF vaccine used on fourteen patients with pancreatic cancer whose tumors had been surgically removed. The patients received varying amounts of vaccine eight weeks after their surgeries. Twelve of the patients also received six months of chemotherapy and radiation therapy. One month following the chemotherapy and radiation, six patients who were in remission received additional vaccinations. Three patients receiving one of the higher vaccine dosages showed immunity to their tumor cells and experienced a disease free survival time of at least 25 months following their diagnosis. The researchers concluded that the vaccine is safe and without side effects, and the response dose-dependent. (Jaffee, Hruban et al. 2001)

An article published in *International Journal Cancer* presented the results of a clinical trial involving forty-eight patients with pancreatic cancer that were vaccinated by injection of synthetic mutant Ras peptides in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF). Peptide-specific immunity was induced in 25 of 43 (58%) patients, indicating that the vaccine used is very potent and capable of eliciting immune responses even in patients with end-stage disease. Patients with advanced cancer demonstrating an immune response to the peptide vaccine showed prolonged survival (an average of 148 days) from the start of treatment compared to non-responders (average survival of 61 days). (Gjertsen, Buanes et al. 2001)

## **Onyx-015**

Onyx scientists have developed a recombinant adenovirus that destroys malignant tissue while sparing normal cells. The Onyx-015 (CI-1042) Phase I and II pancreatic trials have been closed and results are pending. This drug is made by Onyx Pharmaceuticals and is being tested at the University of California-San Francisco.

Onyx Pharmaceuticals

Phone: (510) 222-9700

Fax: (510) 222-9758  
[www.onyx-pharm.com](http://www.onyx-pharm.com)

### ***TNP-470***

A recent study investigated the effects of the angiogenesis inhibitor TNP-470 on human pancreatic cancer cells in vitro and in vivo. Treatment with TNP-470 significantly reduced new angiogenesis in tumors of all three human pancreatic cancer cell lines. TNP-470 reduced tumor growth and metastatic spread of pancreatic cancer in vivo. This was probably due to the anti-proliferative effect of the agent on endothelial cells rather than to the direct inhibition of pancreatic cancer cell growth. (Hotz, Reber et al. 2001)

Tap Pharmaceuticals  
Phone: (800) 621-1020

### ***R115777***

Pancreatic cancer cells often proliferate via the farnesyl transferase pathway. The Ras protein attaches to the inner cell membrane through a lipid (fat) called farnesyl. The first attachment step is catalyzed by the enzyme farnesyl transferase. After attachment, the Ras protein is phosphorylated by tyrosine kinase which activates other kinases in a chain of events that stimulates cell growth. Mutant Ras proteins continuously stimulate cell growth causing excessive cell proliferation resulting in tumors.

An experimental drug called R115777 functions as a specific farnesyl transferase inhibitor. Clinical trials are being conducted by the National Cancer Institute (NCI). (Prevost, Pradines et al. 1999)

National Cancer Institute  
Phone: (301) 496-4891

## **Innovative Drug Strategies**

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

- Statin drugs, such as Lovastatin
- COX-2 inhibitors, such as Lodine, Nimesulide and Sulindac
- Metformin, a drug use in Europe for diabetes

There is evidence in the scientific literature that the proper combination of cell differentiating agents and chemotherapy may slow the progression of pancreatic cancer. In order to have a realistic chance of achieving a significant remission, the use of experimental therapies is highly recommended. This article succinctly describes some of the promising new therapies currently being studied. A more detailed description can be found in the Molecular Oncology section of the Life Extension Foundation's Cancer Treatment protocol.

### ***Statin Drugs***

Statins have been found to have a number of beneficial effects beside their ability to lower plasma LDL-cholesterol. Statin drugs been found to reduce the markers of inflammation. Statins,

and particularly lipophilic statins, in general inhibit cell proliferation, seemingly by multifaceted mechanisms, including:

- inhibition of cell cycle progression
- induction of apoptosis (programmed cell death)
- reduction of cyclooxygenase-2 activity
- enhancement of angiogenesis (new blood vessel growth)
- inhibition of G protein prenylation through a reduction of farnesylation and geranylgeranylation by inhibition of the synthesis of a number of small prenylated GTPases (which are derived from cholesterol and mevalonate) involved in cell growth, motility, and invasion. (Sumi, Beauchamp et al. 1992; Sumi, Beauchamp et al. 1994)

This effect has been used to show that statins are anti-carcinogenic in vitro and in animals. (Davignon and Mabile 2001)

#### LOVASTATIN

Lovastatin was shown to inhibit proliferation of two pancreatic carcinoma cell lines with p21-Ras oncogenes. (Muller, Bockhorn et al. 1998)

A study published in the journal *Gastroenterology* showed that Lovastatin augmented, by up to fivefold, the cancer cell-killing effect of Sulindac, a drug with COX-2 inhibiting properties. In this study, three different colon cancer cell lines were killed (made to undergo programmed cell death) by depriving them of COX-2. When Lovastatin was added to the COX-2 inhibitor, the kill rate was increased by up to five times. (Agarwal, Rao et al. 1999)

An article published in the journal *Cancer Research* examined the effects of two HMG-CoA reductase inhibitors (Fluvastatin and Fovastatin) on in vitro invasion of human pancreatic cancer PANC-1 cells. The results suggest that HMG-CoA reductase inhibitors affect RhoA translocation and activation by preventing geranylgeranylation, which results in inhibition of Epidermal growth factor (EGF)-induced invasiveness of human pancreatic cancer cells. (Kusama, Mukai et al. 2001)

#### **COX-2 Inhibitors**

Cyclooxygenase, also referred to as prostaglandin endoperoxide synthase, is an enzyme that converts arachadonic acid into prostaglandins, thromboxanes and other eicosanoids. Cyclooxygenase-1 (COX-1) forms prostaglandins that stimulate the synthesis of protective mucous in the stomach and small intestines. Cyclooxygenase-2 (COX-2) is induced by tissue injury and leads to inflammation and pain. Several types of human tumors over-express COX-2 but not COX-1, and experiments demonstrate a central role of COX-2 in experimental tumor genesis. COX-2 produces prostaglandins that inhibit apoptosis and stimulate angiogenesis. Non-selective NSAIDs inhibit both COX-1 and COX-2 and can cause platelet dysfunction, gastrointestinal ulceration, and kidney damage. Selective COX-2 inhibitors, such as meloxicam, celecoxib (SC-58635), and rofecoxib (MK-0966), are NSAIDs that have been modified chemically to preferentially inhibit COX-2 but not COX-1 and are currently being investigated for use in cancer treatment. (Fosslien 2000)

Based on the promising research, The Life Extension Foundation began in 1997 to recommend the European COX-2 inhibiting drug nimesulide to cancer patients. Since then a wealth of clinical research has confirmed that COX-2 is elevated in many cancers, including pancreatic cancer and that COX-2 inhibitors are useful in treating cancer.

An article published in the journal *Cancer Research* showed that COX-2 levels in pancreatic cancer cells are 60 times greater than in adjacent normal tissue. (Tucker, Dannenberg et al. 1999)

A study published in the journal *Cancer Research* found COX-2 expression in 14 of 21 (67%) pancreatic carcinomas. Two non-steroidal anti-inflammatory drugs, sulindac sulfide and NS398, produced a dose-dependent inhibition of cell proliferation in all pancreatic cell lines tested. (Molina, Sitja-Arnau et al. 1999)

An article published in the journal *Clinical Cancer Research* found a strong expression of COX-2 protein was present in 23 of 52 (44%) pancreatic carcinomas, a moderate expression was present in 24 (46%), and a weak expression was present in 5 (10%). In contrast, benign tumors showed weak expression or no expression of COX-2, and only islet cells displayed COX-2 expression in normal pancreatic tissues. (Okami, Yamamoto et al. 1999)

A recent article published in the journal *Anticancer Research* evaluated the general COX inhibitor indomethacin and the COX-2 specific inhibitor NS-398 on four pancreatic cancer cell lines. Both agents inhibited cellular proliferation and growth and induced apoptosis (programmed cell death). (Ding, Tong et al. 2000)

A study published in the journal *Cancer Research* examined the mechanism of NSAIDs on COX-2 gene expression. The authors present evidence that NSAIDs have a complicated effect on phospholipase enzymes which result in depriving COX-2 of its substrate, arachadonic acid, which is needed to manufacture inflammatory prostaglandins. (Yuan, Mandal et al. 2000)

A more recent article published in the journal *Cancer* examined 70 surgically resected pancreatic cancers at the National Cancer Center Hospital in Tokyo. Marked COX-2 expression was observed in 57% (24 of 42) of pancreatic duct cell carcinomas, in 58% (11 of 19) of adenomas, and in 70% (7 of 10) of adenocarcinomas of intraductal papillary mucinous tumors. All four pancreatic cancer cell lines expressed COX-2 protein weakly or strongly, and the inhibitory effect of aspirin on cell growth was correlated with the expression of COX-2. (Kokawa, Kondo et al. 2001)

## LODINE

Lodine XL is an arthritis drug approved by the FDA that interferes with COX-2 metabolic processes. The maximum dosage for Lodine is 1000 mg daily. The most convenient dosing schedule for the patient involves the prescribing of two Lodine XL 500-mg tablets in a single daily dose. As with any non-steroidal anti-inflammatory drug (NSAID), extreme caution and physician supervision are necessary. The most common complaints associated with Lodine XL use relate to the gastrointestinal tract. Serious GI toxicity such as perforation, ulceration, and bleeding can occur in patients treated chronically with NSAID therapy. Serious renal and hepatic reactions have been rarely reported. Lodine XL should not be given to patients who have previously shown hypersensitivity to it or in whom aspirin or other NSAIDs induce asthma,

rhinitis, urticaria, or other allergic reactions. Fatal asthmatic reactions have been reported in such patients receiving NSAIDs.

#### NIMESULIDE

Nimesulide is a safer COX-2 inhibitor approved for use in foreign countries, but not currently approved by the FDA. Several studies have shown Nimesulide to be useful in controlling the pain associated with cancer. (Gallucci, Toscani et al. 1992; Corli, Cozzolino et al. 1993; Toscani, Gallucci et al. 1993)

Nimesulide is available from Mexican pharmacies or can be ordered by mail from European pharmacies. The suggested dose for nimesulide is two 100-mg tablets a day.

#### CELECOXIB

Celecoxib (Celebrex, croscarmellose sodium) is a newly approved COX-2 inhibitor that is approved for use to relieve the signs and symptoms of rheumatoid arthritis and osteoarthritis. Recently published articles describe experiments where Celecoxib was shown to be effective in preventing several drug-induced cancers.

In an article published in the journal *Oncology Reports*, Celecoxib, given daily in the diet, significantly inhibited the induction of rat mammary tumors by 7, 12-dimethylbenz(a) anthracene (DMBA). Tumors continued to grow actively in control rats fed chow diet only. In contrast, the Celecoxib-supplemented diet significantly decreased the size of the mammary tumors over the 6 week treatment period, resulting in an average reduction in tumor volume of approximately 32%. Tumor regression occurred in 90% of the rats. In addition, new tumors continued to emerge in the control group, in contrast to their significantly decreasing numbers in the Celecoxib treated group over the same time period. (Alshafie, Abou-Issa et al. 2000)

Another article published in the journal *Cancer Research* described an almost identical experiment with Celecoxib and ibuprofen fed rats with mammary tumors induced by DMBA. Dietary administration of celecoxib produced striking reductions in the incidence, multiplicity, and volume of breast tumors relative to the control group (68%, 86%, and 81%, respectively;  $P < 0.001$ ). Ibuprofen also produced significant effects, but of lesser magnitude (40%, 52%, and 57%, respectively;  $P < 0.001$ ). (Harris, Alshafie et al. 2000)

Because ultraviolet (UV) light can induce COX-2 and non-specific NSAIDs can decrease UV-induced skin cancer, Celecoxib (a specific COX-2 inhibitor) and indomethacin (a nonspecific NSAID), were evaluated for their ability to block UV-induced skin tumor development in hairless mice. Mice fed celecoxib showed a dose-dependent reduction (60% and 89%, respectively) in tumor yield. Indomethacin reduced tumor yield by 78%. The authors concluded that “The dramatic protective effects of celecoxib suggests that specific COX-2 inhibitors may offer a way to safely reduce the risk of skin cancer in humans.” (Fischer, Lo et al. 1999)

In an article published in the journal *Carcinogenesis*, Celecoxib reduced the number and multiplicity of skin cancers induced by UV light by 56% as compared to the controls. (Pentland, Schoggins et al. 1999)

Celecoxib was also shown to inhibit the formation of colon tumors in rats induced by the drug azoxymethane. Celecoxib added to the diet inhibited both incidence and multiplicity of colon tumors by about 93 and 97%, respectively. It also suppressed the overall colon tumor burden by more than 87%. (Kawamori, Rao et al. 1998)

## SULINDAC

Sulindac is an anti-inflammatory, non-steroidal drug (NSAID) that has been shown to have a protective effect against the incidence and mortality of colorectal cancer.

An article published in the journal *Carcinogenesis* reported that Sulindac (and two other COX inhibitors indomethacin and NS-398) inhibit cell growth in both COX-2-positive and COX-2-negative pancreatic tumor cell lines. (Yip-Schneider, Barnard et al. 2000)

A recent study showed that treatment with both Sulindac and green tea extract significantly reduced the number of tumors in mice with multiple intestinal neoplasia. The study also reported that green tea and sulindac alone resulted in a reduction in the number of tumors. The goal of the researchers was to find a nontoxic therapy for cancer prevention and treatment. (Suganuma, Ohkura et al. 2001)

We thus suggest that physicians consider prescribing a COX-2 inhibitor and a statin drug to pancreatic cancer patients (in addition to other therapies) for a period of 3 months. Here are 2 dosing schedules we suggest:

- 1000 mg a day of Lodine XL, and
- 80 mg a day of Mevacor (lovastatin) or Lipitor

Blood tests to assess liver and kidney function are critical in protecting against potential side effects. To ascertain efficacy, regular CA-19.9 serum tests and imagery testing are suggested.

## SILYMARIN, CURCUMIN

Both silymarin (found in the herb milk thistle) and curcumin (found in the spice turmeric) are selective inhibitors of cyclooxygenase (COX) and may be beneficial in preventing and treating pancreatic cancer. (Cuendet and Pezzuto 2000)

## **Metformin**

Metformin is a drug used to treat diabetes that has been used for over 20 years in Canada and Europe and more recently in Japan. Metformin lowers elevated glucose levels, but does not cause hypoglycemia in non-diabetic patients. Metformin is available from the FDA only for diabetic patients with severe symptoms that are not controlled by diet and cannot take insulin.

In an article published in the journal *Pancreas*, the effect of islet hormones on pancreatic cancer cells in vitro was investigated. Insulin (but not somatostatin and glucagon) induced pancreatic cancer cell growth. Insulin also significantly enhanced glucose utilization of pancreatic cancer cells before it enhanced cell proliferation. These findings suggest that insulin stimulates proliferation and glucose utilization in pancreatic cancer cells. (Ding, Fehsenfeld et al. 2000)

In a recent study published in the journal *Gastroenterology*, Metformin was investigated. Two groups of high fat-fed hamsters were used. One group received Metformin in drinking water for

life, and the other group served as a control. All hamsters were treated with a known pancreatic carcinogen. Although 50% of the hamsters in the high-fat group developed malignant lesions, none was found in the Metformin group. Also, significantly more hyperplastic and pre-malignant lesions, most of which were found within the islets, were detected in the high-fat group (8.6 lesions per hamster) than in the high-fat and Metformin group (1.8 lesions per hamster). The authors propose that this mechanism may explain the association between pancreatic cancer and obesity, which is usually associated with peripheral insulin resistance. (Schneider, Matsuzaki et al. 2001)

## **Alternative Treatments**

### **Spes**

The September 17, 1998 issue of the *New England Journal of Medicine* published a study on a product called PC Spes that was 100% effective in reducing PSA levels in advanced prostate cancer patients. The company that makes PC Spes to treat prostate cancer also makes a herbal preparation to treat breast and certain other cancers called Spes. The Spes preparation has been shown effective in the 4 years that Foundation members have been using it.

The studies show that Spes works best against cancers with a mutated p53 oncogene and an over-expressed N-RAS gene, both of which are associated with pancreatic cancer. Cancer patients have been getting good results when combining Spes with high-dose genistein, soy extract, curcumin, and an 83% green tea extract. What follows is a highly technical description of the molecular mechanisms of action of Spes. Please don't be intimidated if you can't understand all of this as it is written to inform the oncologist as well as the lay person.

Spes has been shown to inhibit prostaglandin E2 (PGE2) by about 50%. Cancer patients often develop high concentrations of PGE2 that can promote the proliferation of some cancer cell lines and also damage immune function. PGE2 inhibits the T cell response, causes a decrease in natural killer (NK) cells, and inhibits lymphokine production. PGE2 enhances tumor survival by blocking the natural destruction via the lysis process of tumor cells. In addition, PGE2 promotes abnormal platelet aggregation, a common feature that enables cancer cells to enter the interstitial tissue through a blood vessel wall to establish metastatic sites. PGE2-induced endothelial cell damage attracts metastatic cancer cell colony formation. Many cancer patients succumb to acute death when an abnormal blood clot (thrombus) causes a heart attack or stroke. It is clearly desirable to suppress PGE2, and Spes does this by about 50%. The suppression of PGE2 by Spes has shown a dramatic increase in NK activity. While cancer drugs are in development that work by suppressing PGE2 formation, Spes is available as a dietary supplement for use today.

Nearly all cancer cells secrete a peptide hormone called substance P that promotes tumor growth. Substance P also functions as a neurotransmitter involved in pain pulse transmission through the nerves. Spes appears to lower the levels of substance P, thus potentially slowing tumor growth and alleviating pain.

Spes increases enkephalin production. Enkephalins are peptides produced in the brain that act as opiates, binding to receptor sites involved in pain perception. This could be a mechanism by which Spes alleviates pain. Spes may increase enkephalins between 30 to 50% in about 1 hour.

Beta-Endorphin levels are markedly depressed in the cerebrospinal fluid of cancer patients. Endorphins are polypeptides produced in the brain that also act as opiates producing an analgesic effect by binding to opiate receptor sites. The most active of the endorphins is beta-endorphin. Spes has been shown to normalize beta-endorphin levels. Another mechanism by which Spes provides analgesic action is by lowering norepinephrine in relation to serotonin. Spes raises acetylcholine levels in the brain by an average of 60.4%. This also has a positive effect on pain reduction.

Spes increases cAMP (adenosine 3N,5N-cyclic monophosphate) by a dramatic 150%, but has only a modest effect on cGMP (cyclic guanosine monophosphate). This induces a hyperpolarization of the post-synaptic membranes, inducing an inhibition of the pain signal transmission, but not a blockage of the opium receptors. High levels of cAMP also normalize mitosis, that is cell division. Thus, spes may promote cell differentiation and inhibit abnormal cell growth via its effects on cAMP and cGMP.

Spes reduces the afferent peripheral pain signals and increases the central pain-modulating function. This is a fancy way of saying Spes causes a reduction in internal organ pain or bone pain.

In the animal model, Spes was directly injected into the tumor site and caused an inhibition rate of 133% in tumor weight or volume. On hepatocarcinoma cell lines, Spes markedly reduced the number of survived cells in a total unit area, reversed the self-keeping system of the cancer cells, and caused the differentiation of the cancer cells to normal cells. By causing the cancer cells to differentiate normally, Spes may markedly inhibit the advancement of the tumor.

Alpha-Fetoprotein (AFP) is a specific marker for gene expression in hepatocellular carcinoma. AFP is a serum protein produced by the fetal liver and yolk sac during prenatal development and reaches its full expression at 15 weeks of gestation, falling rapidly thereafter until normal adult levels are reached. High levels in an adult is an indication of hepatocellular carcinoma. Spes was shown to block expression of AFP by 83.5%.

The N-Ras gene is a "transforming" gene whose over-expression is required for the activation of hepatocellular carcinoma and approximately 30% of all other cancers. A mutation in the N-Ras gene tends to turn off the switch for cell cycle progression. N-Ras thus interacts with other proteins and simulates cell growth. Spes was shown to block the over-expression of N-Ras gene.

Ribosomal RNA instructs specific ribosomes to join into a group called ribosomal complex. This is the production facility for making protein. A ribosome is a cell organelle. It is the site of amino acid assembly in the exact sequence ordered by messenger RNA (mRNA). mRNA receives instructions (the genetic code) in the nucleus for the exact sequence of the 22 different amino acids necessary to make a specific protein. This process is called transcription. It is at this point that over-expression often occurs and that the cell turns cancerous. IGF-II has a growth promoting effect on cells and Spes blocks the over-expression of mRNA for IGF-II synthesis.

Finally, Spes increases SOD production in the blood serum by 50% and suppresses free radical generation.

Dosage recommendations are based on body weight. Under 150 lbs., two capsules 2 hours prior to breakfast on an empty stomach and again two capsules 2 hours prior to dinner on an empty stomach. Over 150 lbs. of body weight, three capsules 2 hours prior to breakfast on an empty

stomach and again three capsules two hours prior to dinner on an empty stomach. An empty stomach means no food or any other medication or supplement during the 2-hour period. Spes requires a noncompetitive stomach environment for proper absorption.

The pain relieving effect should be felt within 2 hours. Also, mood and appetite should improve as well. Botaniclab, the manufacturer of the product, claims that Spes works as well as hydrazine sulfate in countering the cachexia that occurs in late-stage cancer. Testing for blood tumor markers and tumor volume should be done regularly to determine if Spes is effective against the individual's cancer.

Spes is a proprietary blend of the following herbs: *Agrimonia pilosa* Ledeb (Agrimony), *Cervus nippon* Temminck (Deer antler), *Corydalis bulbosa*, *Ganoderma japonicum* (Reishi), Panax ginseng (Korean ginseng), bee pollen, *Glycyrrhiza glabra* (licorice), *Lycrois radiata*, *Pyrola rotandifolia*, *Rabdosia rubescans*, *Stephania delavayi*, *Stephanica sinica*, and *Zanthoxylum nitidium*.

The following are excerpts from articles on some of these herbs that pertain to their anti-cancer or immune-modulating properties.

#### AGRIMONY

In a preliminary study, the herb agrimony was shown to have anti-tumor activity against several transplantable rodent tumors. (Koshiura, Miyamoto et al. 1985)

Agrimoniin, a tannin present in agrimony, has been shown to be a novel cytokine inducer for interleukin-1, which is used for its anti-tumor properties. Agrimoniin also has been shown to have inhibitory effects on tumors in mice. (Miyamoto, Kishi et al. 1987; Murayama, Kishi et al. 1992)

#### REISHI

Polysaccharides from fresh fruiting bodies of *Ganoderma lucidum* have been shown to have strong beneficial effects on the immune system. In a study published in the *International Journal Cancer*, levels of interleukin-1 beta, tumor necrosis factor-alpha, and interleukin-6 in macrophage cultures treated with *Ganoderma* polysaccharides were between 5 and 29 times higher than those of untreated controls. (Wang, Hsu et al. 1997)

*Ganoderma* also has significant antioxidant properties. The amino-polysaccharide fraction from *Ganoderma lucidum* was shown to significantly inhibit iron-induced lipid peroxidation in rat brain homogenates and showed a dose-dependent inactivation of hydroxyl radicals and superoxide anions. (Lee, Kwon et al. 2001)

#### KOREAN GINSENG

Long-term administration of ginseng with mice has been shown to reduce the incidence and inhibit the growth of tumors induced by various chemical carcinogens, including DMBA, urethane and aflatoxin. (Yun, Yun et al. 1983)

Panax ginseng has been shown to enhance many immune functions including T-cell activity, interferon production and macrophage activity. (Scaglione, Ferrara et al. 1990) (Xiaoguang, Hongyan et al. 1998)

Spes is available from the Life Extension Foundation as an adjuvant natural therapy by calling 1-800-544-4440.

### ***Digestive Enzymes***

In an extraordinary study by Dr. Nicholas Gonzalez, 11 patients with pancreatic cancer were treated with large doses of pancreatic enzymes, nutritional supplements, "detoxification" procedures including coffee enemas, and an organic diet. Of the 11 patients, 9 (81%) survived one year, 5 (45%) survived two years, and 4 have survived three years. At the time the study was published, two patients were alive and doing well: one at three years and the other at four years. This pilot study suggests that an aggressive nutritional therapy with large doses of pancreatic enzymes led to significantly increased survival over what would normally be expected for patients with inoperable pancreatic cancer. (Gonzalez and Isaacs 1999)

The concept of using pancreatic digestive enzymes to treat cancer was first proposed by Dr. John Beard who published "The Enzyme Theory of Cancer" in 1911. Enzyme therapy was largely forgotten after his death in 1923, except for a few alternative therapists. While in medical school, Dr. Gonzalez met Dr. William Donald Kelley, a Texas dentist who had been treating cancer patients with enzymes for over twenty years. After reviewing his medical records, Dr. Gonzalez found many cases that had followed Dr. Kelly's program and lived far beyond what would be expected with this disease. In comparison, a recent trial of 126 patients with pancreatic cancer treated with the newly approved drug, gemcitabine, reported that not a single patient lived longer than 19 months.

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 clinical trial comparing Dr. Gonzalez's nutritional therapy against gemcitabine in the treatment of inoperable pancreatic cancer. This study has full FDA approval and is being conducted under the Department of Oncology and the Department of Surgical Oncology at Columbia Presbyterian Medical Center in New York. To learn more about the study and its objectives, call Michelle Gabay, R.N., in the office of John Chabot, M.D., Chief of Surgical Oncology at Columbia, phone (212) 305-9468.

### ***Monoterpenes***

Monoterpenes are non-nutritive dietary components found in the essential oils of citrus fruits and other plants. A number of dietary monoterpenes have anti-tumor activity. Several mechanisms of action may account for the anti-tumor activities of monoterpenes, including:

- induction of hepatic Phase II carcinogen-metabolizing enzymes, resulting in carcinogen detoxification.
- induction of apoptosis (programmed cell death)
- inhibition of cell growth by inhibiting the prenylation of Ras and other proteins

- suppression of hepatic HMG-CoA reductase activity, a rate-limiting step in cholesterol synthesis

Monoterpenes appear to act through multiple mechanisms in the prevention and chemotherapy of cancer. Several researchers are investigating these mechanisms and finding that, although the exact mechanism was not what they had assumed, the monoterpenes, limonene and perillyl alcohol, have a profound anti-tumor activity on pancreatic cancer. (Elson and Yu 1994; Gelb, Tamanoi et al. 1995; Crowell, Siar Ayoubi et al. 1996; Gould 1997; Bardon, Picard et al. 1998; Crowell 1999)

#### LIMONENE

In an article published in the journal *Anticancer Drugs*, the growth inhibitory effects of limonene and other monoterpenes (including perillyl alcohol) on pancreatic carcinoma cells carrying a K-Ras mutation were examined. Limonene caused an approximately 50% growth reduction. The authors concluded that although effective in inhibiting the growth of tumor cells harboring activated Ras oncogenes, limonene and perillyl alcohol are unlikely to act by inhibiting Ras function. (Karlson, Borg-Karlson et al. 1996)

#### PERILLYL ALCOHOL

Perillyl alcohol is a monoterpene consisting of two isoprene units manufactured in the mevalonate pathway. It is found in small concentrations in the essential oils of lavender, peppermint, spearmint, sage, cherries, cranberries, perilla, lemongrass, wild bergamot, gingergrass, savin, caraway and celery seeds. (Belanger 1998)

In an article published in *Cancer Letters*, perillyl alcohol was shown to reduce the growth of pancreatic tumors injected into hamsters to less than half that of controls. Moreover, 16% of pancreatic tumors treated with perillyl alcohol completely regressed, whereas no control tumors regressed. (Stark, Burke et al. 1995)

Perillyl alcohol and perillic acid are metabolites of limonene. Limonene is only a weak inhibitor of the isoprenylation enzymes of Ras and other proteins, whereas perillyl alcohol and perillic acid are more potent inhibitors. (Hardcastle, Rowlands et al. 1999)

One study of perillyl alcohol found that Ras prenylation by farnesyl protein transferase (FPTase) was inhibited by 17% and RhoA prenylation by geranylgeranyl protein transferase (GGPTase) was inhibited by 28%. FPTase and GGPTase are the two enzymes involved in the process of attaching Ras proteins to the inner membrane of the cell. By inhibiting this first step, the mutated Ras proteins are not able to continuously stimulate cell growth causing excessive cell proliferation resulting in tumors. (Broitman, Wilkinson et al. 1996)

Further investigation into the effect of perillyl alcohol on prenylation enzymes, however, found that perillyl alcohol inhibited farnesylation and MAP kinase phosphorylation in H-Ras, but not in K-Ras. (Stayrook, McKinzie et al. 1998)

Perillyl alcohol induces apoptosis without affecting the rate of DNA synthesis in both liver and pancreatic tumor cells. (Crowell, Siar Ayoubi et al. 1996)

In an article published in the journal *Carcinogenesis*, Staybrook et al. concluded that the inhibitory effects of perillyl alcohol on pancreatic cell growth was due to a stimulation of apoptosis by increasing the pro-apoptotic protein Bak. (Staybrook, McKinzie et al. 1997)

In the first trial phase I trial of perillyl alcohol, 18 patients with advanced malignancies were treated with perillyl alcohol three times daily. One patient with ovarian cancer experienced a decline in CA-125, and several others experienced a stabilization of their disease for up to 6 months. Due to the short half-life of the metabolites, a more frequent dosing schedule is recommended. (Ripple, Gould et al. 1998)

In the second phase I trial, perillyl alcohol was administered four times a day. Sixteen patients with advanced refractory malignancies were treated. Evidence of anti-tumor activity was seen in a patient with metastatic colorectal cancer who has an ongoing near-complete response of greater than 2 years duration. Several other patients were on study for greater than or equal to 6 months with stable disease. (Ripple, Gould et al. 2000)

The predominant toxicity of perillyl alcohol seen during both trials were gastrointestinal (nausea, vomiting, satiety, and eructation), which limited the dose.

### ***Borage oil***

Gamma linolenic acid (GLA) is a polyunsaturated fatty acid (PUFA) that has been shown to inhibit the growth and metastasis of a variety of tumor cells, including breast, prostate, and pancreatic cancer. Gamma linolenic acid has also been shown to inhibit angiogenesis, the formation of new blood vessels, which is an essential feature of malignant tumor development.(Cai, Jiang et al. 1999)

GLA treatment has been shown to dramatically change tissue perfusion, especially in liver and pancreatic tumors, even at low doses, and these changes may predict response to GLA therapy. (Kairemo, Jekunen et al. 1997)

In an article published in the British journal *Surgery*, the lithium salt of gamma-linolenic acid (Li-GLA) was tested in mice implanted with pancreatic cancer cells. Administration of Li-GLA into the tumor was associated with a significant anti-tumor effect. (Ravichandran, Cooper et al. 1998; Ravichandran, Cooper et al. 1998)

Gamma-linolenic acid (GLA) has been found to kill about 40 different human cancer cell lines in vitro without harming normal cells. The lithium salt of GLA (LiGLA) was administered intravenously to 48 patients with inoperable pancreatic cancer in two different treatment centers. Analysis of the results showed that the highest doses of LiGLA were associated with longer survival times as compared with the lowest doses. (Fearon, Falconer et al. 1996)

Cyclooxygenase-2 (COX-2) and lipooxygenase inhibitors are being used to interfere with the growth of several different cell lines including pancreatic cancer. One experimental approach is to use the 5-lipooxygenase inhibitor MK886 along with borage oil. Other approaches to suppressing COX-2 could be the use of one of the new COX-2 inhibiting drugs used to treat rheumatoid arthritis or fish oil supplements providing at least 2400 mg of EPA and 1800 mg DHA a day; or importing the drug nimesulide from Europe or Mexico for personal use. (Anderson, Seed et al. 1998)

## **Fish Oil**

Patients with advanced cancer usually experience weight-loss and wasting (cachexia) and often fail to gain weight with conventional nutritional support. Several studies have shown that supplementation with fish oils containing the essential fatty acids EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) have been helpful and may even reverse the cachexia.

A possible mechanism for the effect EPA has on reversing cachexia has been proposed in a recent article published in the journal *Nutrition*. The biological activity of both lipid mobilizing factor (LMF) and protein mobilizing factor (PMF) was shown to be attenuated by eicosapentaenoic acid (EPA). Clinical studies show that EPA is able to stabilize the rate of weight loss and adipose tissue and muscle mass in cachectic patients with pancreatic cancer. (Tisdale 1999)

After three weeks of an EPA-enriched supplement, the body weight of the cancer patients had increased, and the energy expenditure in response to feeding had risen significantly, such that it was no different from baseline healthy control values. (Barber, McMillan et al. 2000)

Twenty patients with pancreatic cancer were asked to consume two cans of a fish oil-enriched nutritional supplement per day in addition to their normal food intake. Each can contained 16.1 grams of protein, and 1.09 grams of EPA. At the beginning of the study, all patients were losing weight at baseline at a median rate of 2.9 kilograms per month. After administration of the fish oil-enriched supplement, patients had significant weight-gain at both 3 and 7 weeks. (Barber, Ross et al. 1999)

Eighteen patients with pancreatic cancer received dietary supplementation orally with fish oil capsules (1 gram each) containing eicosapentaenoic acid (EPA) 18% and docosahexaenoic acid (DHA) 12%. Patients had a median weight loss of 2.9 kilograms per month prior to supplementation. At a median of 3 months after commencement of fish oil supplementation, patients had a median weight gain of 0.3 kilograms per month. (Wigmore, Ross et al. 1996)

Eicosapentaenoic acid (EPA) has been shown to have an inhibitory effect on the growth of several pancreatic cancer cell lines in vitro. There was a time- and dose-dependent decrease in cell count and viability in cultures of pancreatic cancer cells supplemented with EPA. (Lai, Ross et al. 1996)

A number of polyunsaturated fatty acids have been shown to inhibit the growth of malignant cells in vitro. A study published in the British journal *Cancer* showed that lauric, stearic, palmitic, oleic, linoleic, alpha-linolenic, gamma-linolenic, arachidonic, docosahexaenoic and eicosapentaenoic acids all had an inhibitory effect on the growth of human pancreatic cancer cells, with EPA being the most potent. Monounsaturated or saturated fatty acids were not inhibitory. The action of EPA could be reversed with the anti-oxidant vitamin E acetate or with oleic acid. (Falconer, Ross et al. 1994)

## **Soy**

Genistein has potent tumor growth-regulating characteristics. This effect of genistein has been attributed partially to its tyrosine kinase-regulating properties, resulting in cell-cycle arrest and limited angiogenesis. In a study of non-oxidative ribose synthesis in pancreatic cancer cells,

genestein was shown to control tumor growth primarily through the regulation of glucose metabolism.(Boros, Bassilian et al. 2001)

Dietary protease inhibitors, such as the soybean-derived Bowman-Birk inhibitor and chymotrypsin inhibitor 1 from potatoes, can be powerful anti-carcinogenic agents. Human populations known to have high concentrations of protease inhibitors in the diet have low overall cancer mortality rates. (Anonymous 1989)

If the pathology report shows the pancreatic cancer cells to have a mutated p53 oncogene, or if there is no p53 detected, then high-dose genistein therapy may be appropriate. If the pathology report shows a functional p53, then genistein is far less effective in arresting cell growth.

### ***Vitamin E***

Retinol or retinoic acid (vitamin E) is required for insulin release. Retinoids increase transglutaminase activity, and transglutaminase has been implicated in islet insulin release. (Driscoll, Adkins et al. 1997)

A phase II pilot study of 23 patients with pancreatic cancer was conducted to evaluate beta-interferon and retinol palmitate (vitamin E) with chemotherapy. Eight patients responded (35%) and 8 (35%) had stable disease. Median time to progression and survival for all patients were, respectively, 6.1 months and 11 months. Toxicity was high but patients who had responses and disease stabilization had prolonged symptom palliation. (Recchia, Sica et al. 1998)

A new retinoid, mofarotene (RO40-8757), was compared with that of other retinoids on 9 pancreatic cancer cell lines. After treatment with each retinoid, anti-proliferative effect was determined. The authors concluded that mofarotene inhibits the growth of pancreatic cancer cells by inducing G1-phase cell cycle-inhibitory factors (p21, p27, and hypophosphorylated form of Rb protein) and is considered to be a useful agent for pancreatic cancer treatment. (Kawa, Nikaido et al. 1997)

### ***Vitamin D***

In a study reported in the British journal *Cancer*, tumor-bearing mice were given EB 1089, a vitamin D analogue, three times weekly for 4-6 weeks. Tumor growth was significantly inhibited in treated animals compared with controls in the absence of hypercalcemia. (Colston, James et al. 1997)

Vitamin D was shown to inhibit cell growth in pancreatic cancer lines by up-regulating cyclin-dependent kinase inhibitors (p21 and p27). (Kawa, Nikaido et al. 1997)

Vitamin D analogues together with retinoids were shown to inhibit the growth of human pancreatic cancer cells. (Zugmaier, Jager et al. 1996)

A new vitamin D3 analogue, 22-oxa-1,25-dihydroxyvitamin D3 (22-oxa-calcitriol), was tested and found to markedly inhibit the proliferation (3 of 9 cell lines) and cause a G1 phase cell cycle arrest in pancreatic cancer cells. (Kawa, Yoshizawa et al. 1996)

## **Green Tea**

Green tea contains polyphenols, chemicals that act as powerful antioxidants. Epidemiological and human studies have shown varying results for protection against cancer. A review article on green tea stated that “pancreatic cancer studies hint at an inverse association in two of three studies.” (Bushman 1998)

Black and green tea extracts and components of these extracts were examined in vitro for their effect on tumor cell growth. Results showed inhibition (approximately 90%) of cell growth in pancreatic tumor cells by black and green tea extracts (0.02%). Black and green tea extracts also decreased the expression of the K-Ras gene. (Lyn-Cook, Rogers et al. 1999)

An article published in the journal *Pancreas* described two experiments where green tea extract was tested in hamsters with pancreatic cancer. In the first experiment, pancreatic cancer was induced by a drug. Fewer of the green tea extract treated hamsters had pancreatic cancers (54% vs. 33%), and the average number of tumors was less (1 vs. 0.5 per hamster). In the second experiment, pancreatic cancers were transplanted onto the back of hamsters. Tumor growth was similar in both groups until 11 weeks after transplantation when inhibition of tumor growth became apparent in the green tea extract group. At 13 weeks, the average tumor volume in the green tea extract group was significantly smaller than that in the control group. These results demonstrated that green tea extract has an inhibitory effect on the process of pancreatic carcinogenesis and on tumor promotion of transplanted pancreatic cancer. (Hiura, Tsutsumi et al. 1997)

## **Quercetin**

Quercetin, a bioflavonoid found in many vegetables, has been studied for use in many types of cancer, including breast, bladder, and colon cancer. It’s use in pancreatic cancer has yet to be examined, but many of the mechanisms are similar. (Lamson and Brignall 2000)

Quercetin was found to down-regulate the expression of mutant p53 protein in human breast cancer lines to nearly undetectable levels. (Avila, Velasco et al. 1994)

Quercetin has been found to arrest the expression of p21-Ras oncogenes in colon cancer cell lines. (Ranelletti, Maggiano et al. 2000)

A study published in the Japanese journal *Cancer Research* found that quercetin was a potent inhibitor of Cyclooxygenase-2 (COX-2) transcription in human colon cancer cells. (Mutoh, Takahashi et al. 2000)

## **Selenium**

A study published in the journal *Carcinogenesis* tested the effects of beta-carotene and selenium on mice with pancreatic tumors induced by azaserine. The authors found that beta-carotene and selenium have inhibitory effects on pancreatic cancer growth. (Appel and Woutersen 1996)

A diet high in selenium was found to significantly reduce the number of drug-induced pancreatic cancers in female Syrian golden hamsters. (Kise, Yamamura et al. 1990)

Excessive amounts of selenium, however, have been shown to increase the incidence of pancreatic cancer in a few studies, which makes its use controversial. (Birt, Julius et al. 1986; Birt, Julius et al. 1988)

### **Mistletoe**

In a phase I/II study, the effect of mistletoe (Eurixor) treatment was evaluated in 16 patients with pancreatic cancer. Mistletoe was administered twice a week by subcutaneous injection. Apart from one anaphylactic reaction, which necessitated suspension of treatment for a few days, no severe side effects were observed. Eight patients (50%) showed a CT-verified status of “no change” according to World Health Organization criteria for at least 8 weeks. Median survival time in all patients was 5.6 months (range 1.5 to 26.5 months). All except two patients claimed that mistletoe had a positive effect on their quality of life, with an obvious decline only during the last weeks of life. These results indicate that mistletoe can stabilize quality of life, and therefore may help patients to maintain adequate life quality in their few remaining months. (Friess, Beger et al. 1996)

A more recent paper describes a patient with inoperable cancer of the pancreas who developed marked eosinophilia during treatment (on day 22) with injections of *Viscum album* (mistletoe). Furthermore, histology performed on day 28 revealed accumulation of eosinophils in the pancreas. Although the overall clinical course of the patient was rapidly progressive, temporary stabilization of the patient's general condition during mistletoe treatment was observed. (Huber, Barth et al. 2000)

### **Summary**

A careful approach to the pancreatic cancer patient is required due to the severity of the disease. Surgery to remove operable tumors should be performed as quickly as possible.

### **LABS**

Insulin insensitivity (Syndrome X) and glucose metabolism problems should be considered in the diagnosis of this disease. This would include tests for both glucose and insulin levels. If excessive levels of insulin are found, an appropriate strategy should be followed (see the chapter on diabetes).

Cholesterol levels should also be carefully examined, and if elevated the appropriate protocols for hypercholesterolemia should be considered.

### **PRESCRIPTION DRUGS**

The following prescription drugs should be considered:

- Metformin if insulin resistance or diabetes is present
- Lovastatin to inhibit cholesterol formation
- Iodine to inhibit cyclooxygenase-2

## DIET

A sensible approach would begin with a diet suitable for diabetics that restricts simple carbohydrates (such as sugar and grains) and emphasizes complex carbohydrates and proteins. Protein supplements and essential fatty acids (i.e., borage and fish oils) will help by shifting the carbohydrate-protein-fat ratio.

## SUPPLEMENTS

A basic protocol for pancreatic cancer might include the following:

- Spes
- Pancreatic enzymes
- Green tea
- Borage or fish oil
- Genistein
- Curcumin (Turmeric) and Milk thistle
- Quercetin
- A high-quality multiple that includes antioxidants, selenium, beta carotene, and vitamins E and D.
- Perillyl alcohol should be carefully considered

## Conventional Expertise

Some of the most advanced clinical applications of the experimental therapies described so far to treat pancreatic cancer are being conducted at:

University of Virginia Dept of Medicine  
Charlottesville, Virginia  
Contact: Dvorit Samid, M.D. at: 804-243-6747

Rush Presbyterian  
St. Luke's Medical Center Section of Medical Oncology  
Chicago, Illinois  
Contact: K.N. Anderson, M.D. at: 312-942-5906

## For further information

For information about experimental cancer therapies, call 1-800-4-CANCER. Make sure you do not enroll in a study where you may be part of a placebo group or where the potential toxicity of the drug may kill you before the cancer does.

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