

determined to make earlier diagnosis a reality

by KAREN BURBACH

Pancreatic
cancer eludes
detection – but
not for long



TONY HOLLINGSWORTH, PH.D.

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George Watson knows the grim statistics for pancreatic cancer. One in 76 people will develop pancreatic cancer, according to the American Cancer Society. Once diagnosed, a person has less than a 5 percent chance of living more than five years.

Even so, the Chadron (Neb.) State College professor and private practice attorney is determined to beat the odds.

“When you first get the diagnosis, you think it’s terminal,” Watson said. “But there is a percentage who overcome it.”

Watson increased his odds for survival by being eligible for the Whipple procedure (*see sidebar*).

But, researchers at UNMC’s Eppley Cancer Center, led by Tony Hollingsworth, Ph.D., want to increase every patient’s odds by identifying diagnostic markers that detect pancreatic cancer before symptoms appear and when surgical removal is still possible.

“I’ve dedicated my career to making earlier diagnosis of pancreatic cancer a reality,” Dr. Hollingsworth said.

Tissue donated by Watson helps Dr. Hollingsworth and the UNMC team, one of the largest pancreatic cancer research groups in the country. “Anything I can do that helps in the diagnosis and treatment is important for the future,” Watson said.

The National Cancer Institute (NCI) funds three pancreatic cancer programs of excellence – one is at UNMC.

The \$5.3 million, five-year Specialized Program of Research Excellence (SPORE) grant in pancreatic cancer – sought after

by the country’s most prestigious research and medical facilities – funds translational research.

“The SPORE grant earned by Dr. Hollingsworth and his colleagues is an outstanding achievement and important milestone for scientific research at UNMC and the UNMC Eppley Cancer Center,” said Ken Cowan, M.D., Ph.D., director of the cancer center. “The National Cancer Institute continues to recognize the important work being done at the Eppley Cancer Center.”

For Dr. Hollingsworth and his team, there is an unrelenting drive to learn more about the basic biology of pancreatic cancer and study new biomarkers that enable them to diagnose the disease earlier. They also want to better understand the progression of the disease and develop new therapies that extend a patient’s life.

“We’re at the cutting-edge of making a difference in people’s lives,” Dr. Hollingsworth said.

A 6-inch long, spongy organ, the pancreas resembles a pear on its side and helps the body digest food and regular body sugar levels. Cancer occurs when cells in the pancreas develop genetic mutations, which cause cells to grow uncontrollably. Tumors form as these cells accumulate.

“If we could shut down that process, we could significantly extend the patient’s life span,” Dr. Hollingsworth said.

Early detection of the disease, however, is a major hurdle.

The location of the pancreas, deep in the abdomen, hinders early discovery of the disease and, unlike mammography, which provides early detection of breast cancer, there are no screening tools for pancreatic cancer. By the time tumors are found they often measure 1 centimeter or more and have metastasized or spread.

“The disease has to be managed differently,” said UNMC researcher Surinder Batra, Ph.D. “We need a more systematic approach with pancreatic cancer because there’s so little time.”

Watson went to the doctor in February for a nagging ache in his upper stomach. At first, he was treated for acid reflux and indigestion, but nothing changed.

When he became jaundiced, doctors ordered a flurry of tests. The ultrasound and CAT scan showed a tumor on the pancreas.

“I didn’t know much about pancreatic cancer, but knew it was a bad one to get,” Watson said.

Fortunately, the cancer had not spread beyond the pancreas.

Dr. Batra says a simple blood test – one that detects a protein produced by pancreatic cancer – would help alert patients to the disease.

An internationally patented biomarker – first identified by UNMC researchers in 2001 and featured on the April 2007 cover of the *Molecular Cancer Research Journal* – shows promise in the early detection of the disease. Mucin 4, a human gene also

known as MUC4, is associated with the disease progression and can be found in blood and tissue.

A high level of the biomarker, detected through a cost-effective blood test, may mean that cancer is in the body.

“MUC4 expression is strongly associated with the lifespan of patients and could be a new early and specific marker for the diagnosis and prognosis of pancreatic cancer,” Dr. Batra said. “About 80 to 90 percent of pancreatic cancer patients have high levels of MUC4 in tumors, fine needle aspiration biopsies and blood, which that makes it easy for us to diagnose cancer.”

Preliminary studies of the blood test show promise and a validation trial, funded by the NIH RO1 and SPORE grants, is underway. “The results of our trial could help us better manage the disease, determine who should go to surgery, how we should treat the patient and how we might stop or decrease expression,” Dr. Batra said.

MUC4 may not be the only marker, though.

Several of Dr. Hollingsworth’s projects focus on the study of MUC1, a glycoprotein that scientists believe plays an important role in the normal function of the pancreas. MUC1, they have found, interacts with and alters the function of p53, a tumor suppressor gene.

“We want to study the big questions and understand how the tumors invade and metastasize so we can understand why the

“Patients should have hope and take comfort in the fact that there are researchers who care.”

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SPORE grant spawns many projects

The UNMC Eppley Cancer Center’s pancreatic program receives nearly \$15.5 million in external funds, most of which comes from the National Cancer Institute (NCI).

Of that, \$5.3 million is part of a competitive five-year Specialized Program of Research Excellence (SPORE) grant in pancreatic cancer.

The SPORE grant compliments the cancer center’s work with the NCI’s Early Detection Research Network (EDRN) and the UNMC-based Pancreatic Cancer Collaborative Registry. It also supports translational research projects, creates a new core in biostatistical support and provides partial support for UNMC’s tissue bank and unique rapid autopsy program.

The EDRN brings together dozens of institutions to evaluate new ways to test for cancer risk and accelerate the translation of biomarker information into clinical use.

The registry, meanwhile, unites at least 12 centers, including Johns Hopkins University, the University of Pittsburgh, Evanston Northwestern Healthcare and the University of Genoa (Italy), with expertise in pancreatic cancer research. The one-of-a-kind, Web-based registry has collected critical information and biological samples from 1,600 patients to develop prevention and treatment strategies.

UNMC’s tissue bank, directed by Julia Bridge, M.D., and its unique rapid autopsy program, which allows cancer patients to donate entire organs, help researchers to study the disease.

“The rapid autopsy program allows us to acquire a large volume of rarely obtained tissues,” said Tony Hollingsworth, Ph.D., who directs the program and the volunteer efforts of more than 30 technicians, students, nurses, residents and faculty members. “The program enables us to undertake many studies that are not otherwise possible.”

disease is so deadly,” Dr. Hollingsworth said. “Patients should have hope and take comfort in the fact that there are researchers who care.”

Dr. Hollingsworth’s team helped discover MUC1 years ago. Since then, they have learned that it protects the cell surface and sends information about the cell surface to the nucleus. That information will be used to design tumor vaccines and make better diagnostic tests for pancreatic cancer. Plans already are underway on a clinical trial of an immunotherapy protocol that induces the patient’s immune system to recognize or attack the pancreatic cancer tumor – just as if it was a foreign invader.

Watson’s father, George Watson Sr., had prostate and lung cancer, but there is no known history of pancreatic cancer in his family.

After the diagnosis, Watson and his wife, Kathleen, decided to seek treatment eight hours from home at UNMC’s hospital partner, The Nebraska Medical Center.

“You have to get to a place that deals with pancreatic cancer,” he said. “We’re fortunate here in Nebraska that we have a place.”

Jean Grem, M.D., a nationally known expert in gastrointestinal malignancies, explores novel therapeutic approaches in both colon and pancreatic cancer. She has developed a clinical trial that uses a patient’s molecular profile to determine the best drug therapy for metastatic colorectal cancer.

Plans are underway for a clinical trial to determine whether there is an advantage to using the peptide inhibitor of N-cadherin to reduce

SURINDER BATRA, PH.D.



the growth and spread of tumors and the incidence of metastasis. UNMC researchers have evidence that expression of N-cadherin by human cancer cells results in tumors that are highly aggressive. The peptide inhibitor, however, has reduced the severity of tumors in mice, said UNMC researcher Keith Johnson, Ph.D., who works on the project with Peggy Wheelock, Ph.D., and Dr. Grem.

Another clinical trial will study the effects of a telomerase inhibitor at three levels: in cultured pancreatic cancer cells, in mice bearing pancreatic tumors and in patients with advanced pancreatic cancer.

In cancer cells, an enzyme called telomerase prevents the protective caps at the end of chromosomes, or telomeres, from shortening, which, in normal cells, naturally occurs as we age. Once telomeres get too short, a healthy human cell stops dividing. Cancer cells are immortal, said UNMC researcher Michel Ouellette, Ph.D., because they tend to express telomerase, which prevents the shortening process and allows malignant cells to grow out of control. Researchers hope the telomerase inhibitor limits the lifespan of cancer cells and blocks the regrowth of residual disease after conventional therapy.

That’s the type of news patients like Watson want to hear.

Cancer treatments forced Watson – for the first time in 33 years – to miss this past summer’s student excursion to London. During his career, he has taken more than 800 Chadron State College students abroad on international study programs.

“The trips give students a different perspective of life in general,” he said.

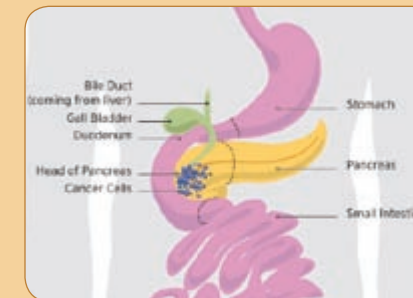
Cancer does the same.

“The diagnosis changes the reality of your life almost immediately,” Watson said. “I have tried to take the outlook that cancer should not alter my life plans, but it does make you more aware of the things that are important and the things that are peripheral.”



AARON SASSON, M.D.

Whipple procedure gives hope to people with pancreatic cancer



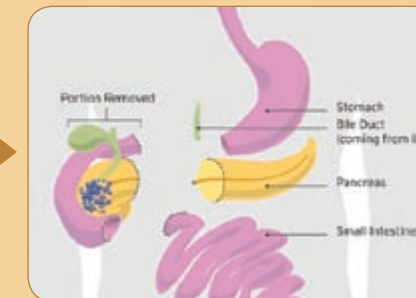
George Watson was fortunate, in that, his cancer had not spread beyond the pancreas.

That silver lining gave him the only chance for a cure.

“The gold standard is to have the Whipple procedure, if possible,” said the father of three.

Only 15 to 20 percent of pancreatic cancer patients are eligible for surgery and, of those, only 15 to 20 percent live five years, said Aaron Sasson, M.D., associate professor of general surgery at UNMC, and chief of GI surgical oncology.

Prior to surgery, Watson underwent an intensive treatment regiment to shrink the tumor that sat near an artery. The regiment included three months of chemotherapy and radiation therapy under the guidance of Jean Grem, M.D., and Chi Lin, M.D.

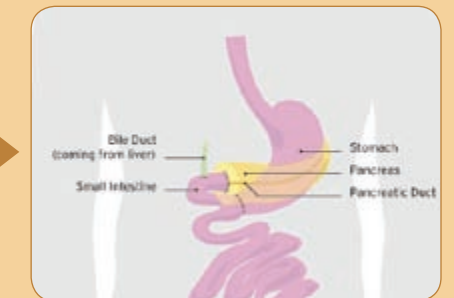


On July 8, Dr. Sasson surgically removed the rest of the growth in a Whipple operation.

Dr. Sasson and his team (Drs. Quan Ly and Chandrakanth Are) are specialists with advanced training in the management of pancreas and hepatobiliary malignancies.

His team takes an intensive approach to surgery, often removing blood vessels that surround the pancreas in order to eradicate the tumor. “Surgery can be quite complicated and last five to seven hours,” Dr. Sasson said.

In the Whipple operation, the head of the pancreas, a portion of the bile duct, the gallbladder and the small intestine is removed. A portion of the stomach also may be removed. Then, the remaining pancreas, bile duct and intestine are sutured back into the intestine.



To ensure the best outcome, the American Cancer Society recommends the Whipple operation be performed in experienced centers, such as The Nebraska Medical Center, that do a high volume of these complex surgical procedures. Dr. Sasson and his team perform more than 50 pancreas operations each year, the majority being Whipples.

The death rate is significantly lower in hospitals that perform a high volume of these procedures, Dr. Sasson said.

“Everything, so far, is good,” Watson said, later during a four-week cycle of chemotherapy. “The prognosis is only as good as the next test.”