The National Pancreatic Cancer Canada Foundation Fund at Princess Margaret Cancer Centre

November 2012

Table of Contents

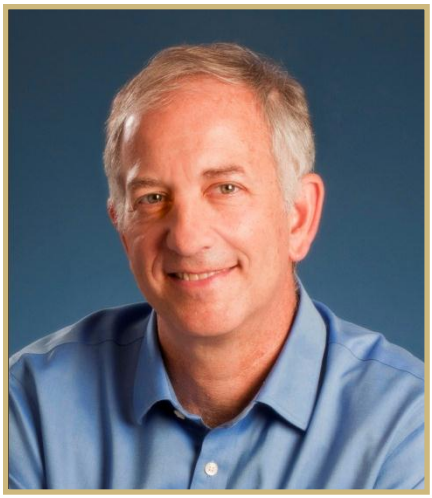
Princess Margaret Cancer Centre and its research arm, Ontario Cancer Institute, have achieved an international reputation as global leaders in the fight against cancer. The Princess Margaret is a member of the University Health Network, which also includes Toronto General Hospital, Toronto Western Hospital and Toronto Rehabilitation Institute. All are research hospitals affiliated with the University of Toronto. For more information, please visit thepmcf.ca.

Your Support

Introduction

Thank you for your ongoing commitment to Princess Margaret Cancer Centre through the **National Pancreatic Cancer Canada Foundation Fund (NPCCF)**.

Over the years, you have contributed to the early detection of pancreatic cancer by providing funds to hire staff and undertake landmark research, including the ongoing development of a unique imaging tool – the MRI Coil. In the following pages, **Drs. Steve Gallinger** and **Malcolm Moore** will update you on how these initiatives are making a difference in the lives of cancer patients.



Dr. Steve Gallinger

The work we are undertaking is perfectly aligned with The Princess Margaret's objective of creating the new gold standard in cancer care: Personalized Cancer Medicine.

This encompasses four main themes:

1) DETECT – finding cancers earlier
2) DIAGNOSE – analyzing cancers more precisely
3) TARGET – targeting treatment more specifically
4) SUPPORT – providing comprehensive physical and emotional support

Dr. Malcolm Moore

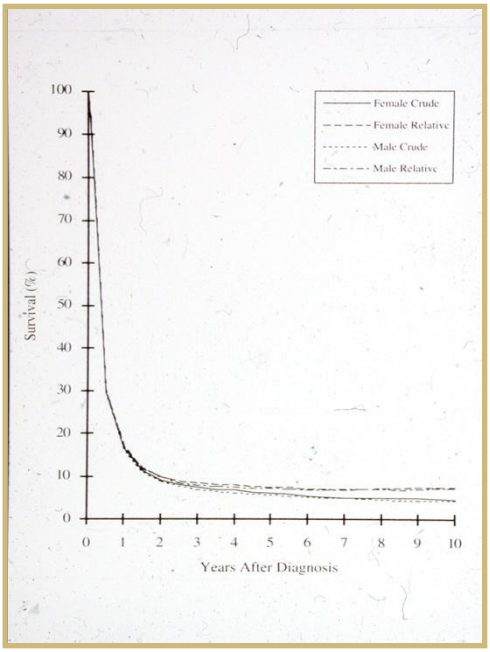
Thank you again for helping us move closer to our goal of conquering cancer in our lifetime.

Your Support

Overview

Pancreatic cancer is the fourth-leading cause of cancer death in Canada, with a five-year survival rate in Ontario of a mere 7%. The lifetime chance of developing pancreatic cancer for the average-risk person is close to 1%. Unlike other common cancers, pancreatic cancer is usually symptom-free, however if there are symptoms, they are non-specific and generally do not occur until later stages of the disease. The lack of symptoms has made diagnosing pancreatic cancer at early stages very difficult.

In our laboratories, and through partnerships with others in the medical community, we continue to conduct research to help us understand risk factors for pancreatic cancer, as well as assess and develop imaging techniques that will help us detect the disease earlier. **The research we have undertaken, with the support of the NPCCF, is reflected in the many studies, presentations and staff hires that are described in this report.**



Pancreatic Cancer Survival

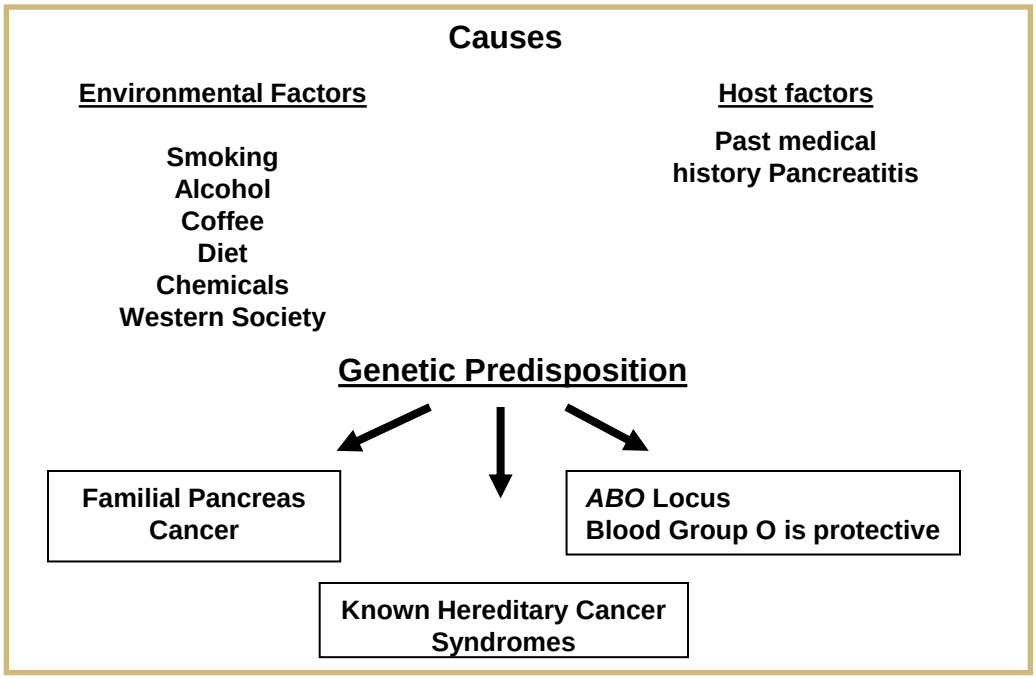
Your Support

Research: 2009 Study

Anderson L, Cotterchio M , Gallinger S. ***Lifestyle, dietary and medical history factors associated with pancreatic cancer risk in Ontario, Canada****. Cancer Causes Control 2009; 20:825-34.*

This paper, reflecting the work undertaken through the support of the NPCCF, examines the connection between pancreatic cancer risk and several lifestyle, dietary and medical history factors. Currently, there is no screening test available for pancreatic cancer and identifying people at high risk (e.g., individuals with a family history of pancreatic cancer or obese persons) may be an important first step in the primary prevention of pancreatic cancer.

Pancreatic adenocarcinoma has one of the worst survival rates of all the cancers. Established risk factors for this malignancy are smoking, body mass index (BMI) and a family history of pancreatic cancer. Possible pancreatic cancer risk factors such as these were evaluated within the population-based Ontario Pancreas Cancer Study.



Your Support

Research: 2009 Study (cont' d)

Overall, 1,740 cases of pancreatic cancer were identified and registered in our Ontario Pancreas Cancer Study (OPCS) between April 2003 and December 2007. Of course, many more cases (about 1,200 each year!) are diagnosed with the disease, however, only a small fraction are well enough to participate in the OPCS. Data for this study was available from 422 eligible cases (45% of contacted living cases). Among the controls, 312 out of 378 (83%) returned the completed questionnaires.

Dr. Michelle Cotterchio

From results of this study, our team discovered that smoking, BMI, family history of pancreatic cancer, and caffeine intake are all risk factors for the disease, while fruit intake and allergy history are associated with a decreased risk.

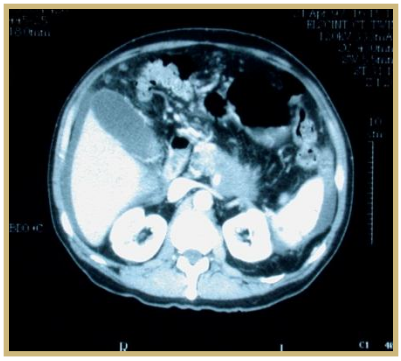
This research adds further support to the associations observed between dietary and lifestyle factors and pancreatic cancer risk, and suggests that interactions might exist between some risk factors and smoking. However, larger studies are needed to explore this premise further.

Dr. Michelle Cotterchio, one of the authors of this study and a world leader in epidemiology research, is a Scientist at Cancer Care Ontario and Associate Professor in the Dalla Lana School of Public Health, University of Toronto. Dr. Cotterchio's research program focuses on the etiology of cancer – in particular breast, colorectal and pancreatic cancer. The majority of her research is focused on modifiable risk factors of breast and colorectal cancer, as well as the interaction with genetic factors. Dr. Cotterchio serves as Co-Principal Investigator on the Ontario Familial Colon Cancer Registry, an international consortium funded by the U.S. National Cancer Institute for the past decade.

Your Support

Research: 2010 Study

Funds from the NPCCF have also been used towards finding effective ways of screening for pancreatic cancer. Since 2003, the goal of the Pancreas Cancer Screening Study (PCSS) has been to find methods of earlier detection to improve the outcome for newly diagnosed cases. Participants in our study included individuals with familial pancreatic cancer (having at least two relatives with pancreas cancer on the same side of the family) or a known hereditary condition that predisposes them to this disease (such as BRCA2 and p16 mutations). In general, screening started at age 50, or ten years younger than the youngest case of pancreas cancer in the family. There were 260 individuals enrolled in the PCSS with subjects returning each year for scans.



Pancreatic cancer - the silent killer

Since this type of cancer is difficult to diagnose, early detection is essential to give patients the maximum chance of a cure. Unfortunately, current commonly used imaging methods, such as CT, cannot detect small cancers and there are radiation hazards associated with yearly CT scans as a screening test. The ideal test would be able to be used repeatedly and safely to screen at-risk patients, in order to detect a high proportion of cancers at an early stage.

In the first few years of the study, both ultrasound and MRI techniques were used to determine their effectiveness for early detection. Recent findings have suggested that a higher resolution MRI may be effective at detecting small pancreatic lesions. Consequently, transabdominal ultrasound was eliminated as part of the study protocol.

To generate an image, an MRI relies on receiver coils, or “antennas”, that are placed around the body. The stronger the signal, the faster a high resolution image can be generated. Unfortunately, when the receiver coils are placed around the body, the pancreas is one of the furthest structures from the skin surface. As a result, spatial resolution of pancreatic imaging is limited, making tumours under 1cm difficult to see.

Your Support

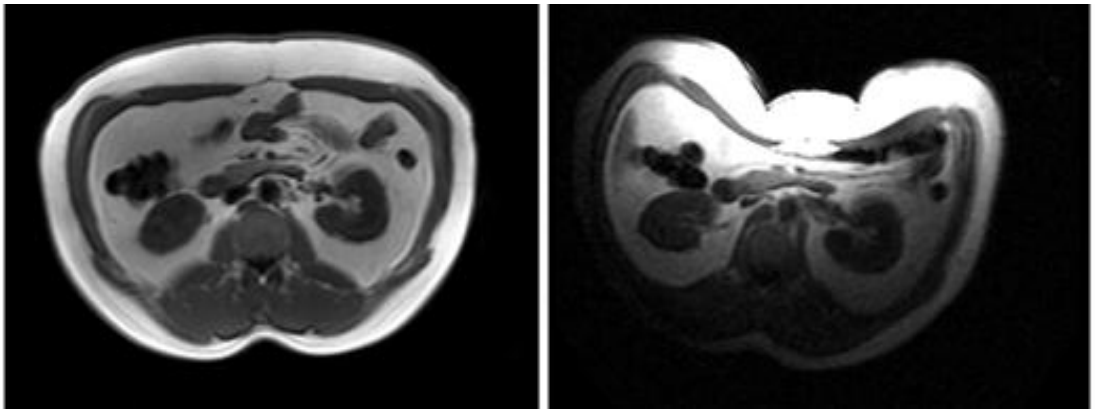
Research: 2010 Study (cont' d)

One method for improving the signal is to increase the field strength of the magnet. This increases the signal by a factor of two. However, the use of high field systems may not make the tumour stand out more. One of the best ways to improve pancreatic cancer detection may be to increase the signal through better receiver coil designs.

Dr. Masoom Haider

University of Toronto Department of Medical Imaging scientists, led by Dr. Masoom Haider, have been developing a new coil for their MRI machine that increases the width and depth of the resulting image. Their initial idea for coil optimization for the pancreas involved developing an external device to compress the abdomen and bring the receiver coils closer to the pancreas. Although this resulted in significant signal improvements, it would likely be less than required for a >3x signal gain without further improvement in receiver coil hardware.

As a result, we have partnered with Sentinelle Medical, a Canadian company specializing in MRI receiver coil design, to increase the signal from the pancreas by a factor of 8-13 or more. This degree of signal gain would allow for sub millimeter resolution pancreatic imaging and a dramatic improvement in image quality.



Compression Improving MRI Signal

Your Support

Research: 2010 Study (cont' d)

The new technology is based on a series of optimizations in the imaging chain, including better coil geometry and better receiver electronics which improve signal reception. From our initial testing, we believe a gain of at least a factor of three can be achieved. We plan to leverage recent advancements in micro-fabrication for improved low-noise coils and low-noise, high performance pre-amplifiers. This technology offers the possibility of significant enhancements in signal-to-noise ratio in clinical MR imaging applications.

In June 2010, we concluded our volunteer testing and also completed the prototype compressive coil with two channels. We have started constructing the new coil which will have multiple channels and further optimization for increased width and depth. We have also begun the protocol optimization on the 3T GE 750 scanner.

*** Please note that research by Dr. Masoom Haider to develop improved receiver coils is ongoing. He will provide an update on the progress of his work at a later date.**

Research: 2012 Study

Screening for pancreatic cancer in a high-risk cohort: an eight-year experience. Al-Sukhni W, Borgida A, Rothenmund H, Holter S, Semotiuk K, Grant R, Wilson S, Moore M, Narod S, Jhaveri K, Haider MA, Gallinger S. J Gastrointest Surg. 2012 Apr;16(4):771-83. Epub 2011 Nov 30

Funds from the NPCCF have more recently been used towards a prospective cohort study on the effectiveness of screening for pancreatic cancer. Taking place between 2003 and 2011, 262 subjects were enrolled in our Toronto study. Participants were chosen based on an elevated estimated lifetime risk for pancreatic cancer due to known genetic mutations and/or cancer family history. Subjects underwent annual magnetic resonance imaging, followed by additional investigations if abnormal findings were detected. Evidence of malignancy or suspicious macroscopic abnormalities prompted referral for surgical intervention.

The average length of follow-up was 4.2 years, during which 84 of the 262 (32%) subjects demonstrated pancreatic abnormalities. Three participants developed pancreatic adenocarcinoma (one 1.5-cm tumour was resected but recurred 2 years later, while the other two subjects developed metastatic cancer), and a fourth participant developed a pancreatic neuroendocrine tumour that was resected. This latter patient is doing well and likely cured. Fifteen subjects had radiologic evidence of branch-duct intraductal papillary mucinous neoplasms, early premalignant lesions, of which two underwent surgical resection. Sixty-five subjects had simple pancreatic cysts that have remained stable.

The results of this study showed that magnetic resonance imaging can detect small pancreatic tumours and cystic lesions, but further improvement in sensitivity is needed. We also determined that an understanding of the natural history of pre-invasive lesions in members of high-risk families is necessary for developing a more effective screening program.

Your Support

Research Staff

In addition to the studies listed above, we recently established a collaboration between our pancreas cancer program and **Dr. Eleftherios Diamandis** at the **Samuel Lunenfeld Research Institute** to identify and characterize novel serum protein biomarkers for the early detection of pancreas cancer. **Our large bank of plasma samples from pancreas cancer patients with all stages of the disease are being used to validate these new biomarkers.**

Dr. Diamandis is an international leader in the study of serum biomarkers in cancer. Along with his graduate student, **Shalini Makawita**, he identified a number of candidate proteins in a small series of samples. Shalini's biomarker research focused on the early detection of pancreatic cancer. **Benefitting from the exposure and training with Dr. Diamandis and The Princess Margaret, she recently co-published (with Dr. Diamandis, Ioannis Prassas, and Caitlin C Chrystoja) the paper, *Bioinformatic identification of proteins with tissue-specific expression for biomarker discovery*, in the journal *BMC Medicine* in April 2012.** Shalini recently left Dr. Diamandis' lab to attend medical school.

There were two additional individuals on our payroll, thanks to your support. **Nicolas Devaud**, is a Chilean surgeon who came to work with me in February 2012. Although he has since returned home, he was working on personalized chemotherapy by studying xenografts of BRCA patients' pancreas tumours in mice. Dr. Devaud worked with **Dr. David Hedley** at The Princess Margaret on this xenograft project.

The other person hired was **Emily Whelan**, a summer student who worked in the laboratory and gained a lot of experience over the past two summers. Emily was involved in the search for the familial pancreas cancer gene. She is now in Halifax, applying to medical school.

Dr. Eleftherios Diamandis; Shalini Makawita, and Dr. David Hedley

Your Support

Research Staff (cont' d)

Thanks to your support, we recently hired an exchange student from China, **Dr. Pin Gao**, who will be spending a year at Princess Margaret Cancer Centre. Dr. Gao is a medical doctor training in surgery, who is currently enrolled in a master's program at Qingdao University. He will be working in our laboratory testing treatments for a type of pancreatic cancer that appears to be unusually sensitive to the chemotherapy drug Cisplatin.

The identification of patients with this subset of pancreas cancer is the result of a new genetic screening program put in place by our team. Dr. Gao will be using tumours that were grown from patients whose cancer has the specific mutation involved. MRI will be an important technique to monitor how the drugs are working, which we hope to later extend to our patients. Dr. Gao will be using the MRI techniques that are being developed by **Dr. Warren Foltz**, from the Department of Radiation Oncology at The Princess Margaret, as part of the program.

Other additions include **Ayelet Borgida** (OPCS coordinator), and **Rabeya Ibrahim** and **Dionne Thomas** (a replacement for **Samantha Jones**, who was also paid by the NPCCF). Ayelet and Rabeya are OPCS research assistants who recruit new patients into the OPCS, organize MRI screening for PCSS participants, and provide educational resources for patients and family members with pancreas cancer.

Dr. Pin Gao

Dr. Warren Holtz

Ayelet Borgida

Dionne Thomas

Your Support

Future Outlook

The balance of your Fund (please see Fund Report on page 15) is being used to support staff in our Program over the next year as well as help pay for some operating costs (rent, phone, computer leases, etc.) and additional pancreatic studies. Assets for these initiatives will be transferred to the appropriate areas in the upcoming months.

Julia Kim

Money from the NPCCF Fund, for example, will be used to help pay for our administrative assistant, **Julia Kim**, who is actively involved in the triage of pancreatic cancer patients, organizing meetings for our team, assisting fellows, and so much more. Her input is invaluable in helping our Program run.

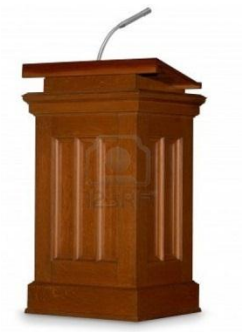
Also supported will be our database manager, **David Chan**, who runs the surgical database at Toronto General Hospital. Maintaining this is vital in helping us study pancreatic cancer surgical results. In fact, we currently have one of our fellows mining the database for an analysis of over 600 Whipple procedures, about half of these for pancreatic cancer.

Dr. Ian McGilvray

Finally, **Dr. Ian McGilvray**, a multi-organ transplant and cancer surgeon at Toronto General, has proposed a trial of pre-operative chemotherapy/radiotherapy, followed by radical surgery for pancreas cancers with involvement of major arteries – arterial resection for cancer of the pancreas (ARCAP). In collaboration with our medical oncology and radiation oncology colleagues at Princess Margaret Cancer Centre, the ARCAP study will be one of its kind worldwide in testing new preoperative chemotherapy and radiotherapy strategies for some of the most difficult operations to resect pancreas cancer. **We will use approximately $150,000 of your fund towards this initiative.**

Your Support

Sharing Our Knowledge



The work we have undertaken over the past few years thanks to your support, has also been reflected in the many presentations we have given. Two presentations that took place in the last month include:

Unravelling the Genetics of Pancreas Cancer *(Goodman Lecture at McGill University) Dr. Steve Gallinger*

Pancreas cancer genetics and the surgeon – should you care? *(Liverpool Lecture at the National Cancer Research Institute - NCRI) Dr. Steve Gallinger*

The focus of these lectures was personalized strategies for pancreatic cancer:

Pancreas cancer remains the most lethal epithelial malignancy with minimal progress in understanding and managing this disease for decades. However, recent technologic advances in high throughput and affordable genomic sequencing are providing novel insights into both germline and somatic tumour genetics which are beginning to impact patient care and outcome.

For example, tumour 'molecular clock' studies have shown that pancreas cancer tumorigenesis is a long process, evolving over many years, thus providing a window of opportunity for screening high risk subjects for earlier stage disease.

Second, new translational insights in BRCA-associated pancreas cancer suggest that these tumours are uniquely sensitive to drugs that take advantage of the somatic homologous recombination DNA repair defect.

Finally, our first 'pass' through the genetic 'catalogue' of driver genes in 100 unselected tumours is yielding findings of relevance for characterizing novel targets to treat patients with more rationale and personalized strategies.

Thank You for Your Support

Thank you

Princess Margaret Cancer Centre is developing and implementing new procedures and setting the gold standard for Personalized Cancer Medicine for patients at The Princess Margaret, across Canada and around the world.

As mentioned previously, one of the key factors in combatting pancreatic cancer is early detection. We hope that our update illustrates the important impact we are making in this area through the **National Pancreatic Cancer Canada Foundation**.

Thank you for your commitment to us.

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