



NETWORK

Ontario Pancreas Cancer Registry

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ONTARIO PANCREAS CANCER STUDY

The Ontario Pancreas Cancer Study (OPCS) aims to identify genetic, environmental and lifestyle causes of **pancreatic adenocarcinoma**, the most common type of pancreas cancer. Results from this study will help us understand risk factors, patterns of inheritance, and discover possible genetic and biochemical markers of pancreas cancer. We are also interested in evaluating pancreas cancer screening techniques with the hope that, in the future, this disease may be detected at an early stage.

The first stage of the OPCS involves obtaining information about family history, cancer treatment, and personal history/lifestyle from a questionnaire package that is mailed to participants. The second stage of the study involves collecting blood (or saliva), medical records, and any available tissue samples from previous biopsies or surgeries. These samples are used to investigate potential sources of genetic risk of pancreas cancer. Genetic counselling is available to every participant. If there is a family history of cancer, genetic counsellors provide information and make referrals for further genetic assessment and possibly genetic testing when appropriate.

The OPCS team greatly appreciates the participation of everyone involved. If you have any questions or would like to be involved with our research, please do not hesitate to contact us. You can also call our toll free number at 1-877-586-1559 and leave a message. We are happy to answer your questions.

NEW WEBSITE LAUNCHED

Fulfilling our commitment to providing support and education to clinicians, patients and their caregivers, we are very proud to announce the launch of the new website for the Zane Cohen Centre (ZCC) for Digestive Diseases - www.zanecohencentre.ca.

A visit to this website offers you a wide range of resources reflecting current breakthrough work in gastrointestinal cancer research carried out by one of the best interdisciplinary teams in the world.

From the home page, you can easily navigate to the OPCS (www.zanecohencentre.ca/gi-cancers/opcs), find information about other diseases and get updates from the research teams.

We have a number of new features, including the ZCCTube, with informative videos highlighting the work of our various team members: www.zanecohencentre.ca/zcc-tube. We look forward to your feedback.

PANCREAS CANCER SCREENING STUDY

As with other types of cancers, early detection is associated with a better prognosis or outcome. Unfortunately, the majority of pancreas cancer cases are diagnosed at late stages. The key to improving survival rates is to identify those who are at high risk of developing the disease and then detecting the disease at the earliest possible stage. Currently, there are no recommended screening strategies for the early detection of pancreas cancer.

The use of pancreas cancer screening is widely debated in the clinical setting as well as in the medical literature. Some studies find that endoscopic ultrasound (EUS) may be a more useful tool to screen for pancreas cancer; however, this has not been proven at this time. Until EUS is widely available in Canada, this is not a feasible option for our study. Recent publications have indicated that contrast-enhanced MRI (magnetic resonance imaging) is more effective at identifying pancreas lesions than non-contrast-enhanced MRI.

From 2003-2011, three screening participants were diagnosed with pancreatic adenocarcinoma. Unfortunately, their tumours were detected at somewhat advanced stages even though they had been participating in annual screening. This suggests the need for a shortened interval between screenings. Therefore, currently enrolled participants will now come every 6 months, instead of annually, for a contrast-enhanced MRI at Princess Margaret Hospital.

To accommodate for the additional time needed to administer intravenous contrast, as well as the need to double the MRIs for our participants, we have restricted the number of participants to the 60 highest risk individuals (under age 75) already enrolled in our program. These individuals are from Familial Pancreas Cancer

THE SEARCH FOR FPC GENES

(FPC) families (two or more biologically-related family members with pancreas cancer) with at least one first-degree relative (parent, child, or sibling) with pancreas cancer, or they have a BRCA2 mutation and at least one first-degree relative with pancreas cancer.

This is the second time that we have changed our screening protocol. Our initial goal in 2003 was to determine the effectiveness of MRI and abdominal ultrasound for early detection of pancreas cancer. In January 2009, we discontinued the use of abdominal ultrasound. This decision was based on our findings that abdominal ultrasound did not detect potentially important pancreas lesions that were identified on MRI.

Since there are no clinical guidelines for pancreas cancer screening, any abnormalities identified through this study may represent findings that would not have been otherwise detected. The major benefit from this study will include improved prognosis and survival of individuals found to have early stage pancreas cancer and the possible development of a clinical screening program for people at high risk of developing this disease.

New enrollment is now closed. For more information, please e-mail fgicr@mtsinai.on.ca or call toll free at 1-877-586-1559 and leave a message. *A generous donation was made by Pancreatic Cancer Canada to the PMH Foundation to support our research in the early detection of pancreatic cancer. For more information, please go to www.pancreaticcancercanada.ca.*



We are pleased to announce the launch of our sister study, the Québec Pancreas Cancer Study (QPCS). The QPCS aims to recruit people with radiologically or pathologically confirmed pancreas cancer and promote pancreas cancer research in Québec. The Principal Investigator is Dr. George Zogopoulos. Participants will be asked to complete family history and personal history questionnaires and donate a blood or saliva sample. Only patients undergoing pancreas resection surgery at the McGill University Health Centre (MUHC) will be asked to donate a small portion of the resection specimen for tumour biology studies. If there is a family history of pancreas cancer, relatives will be invited to participate.

Patients can be referred to the study using a referral form on the QPCS website. The QPCS will contact the patient to obtain informed consent and organize mailing of questionnaires and biospecimen (blood or saliva) collections. Patients will have the opportunity to discuss the study with the Research Coordinator, who is an experienced genetic counsellor and was previously involved with the Ontario Pancreas Cancer Study. The QPCS is also interested in recruiting young (under age 40) and familial cases of biliary, duodenal and colon cancers. Please visit their website www.cancerpancreas.ca for more information.

FPC stands for Familial Pancreas Cancer and refers to families where at least two biologically-related family members have pancreas cancer. The majority of cases of pancreas cancer are random, or sporadic in nature. However, it appears that in some families there are more cases of pancreas cancer than would be expected by chance alone. We suspect that pancreas cancer is strongly hereditary (passed on) in about 5-10% of patients. It is more likely to be hereditary in families where multiple relatives have pancreas cancer, in patients who are diagnosed at young ages (under age 50), or in families where there is a strong family history of certain other types of cancer. Genes have been discovered for hereditary breast/ovarian cancer, hereditary colon cancer and some other types of cancers as well, but not specifically for FPC.

One of the main goals of our pancreas registry is to use exciting new technologies to identify genes causing FPC. We identify patients with a family history of pancreas cancer through referrals, recruitment in clinics/patient wards at Princess Margaret or Toronto General Hospital, or through the Ontario Cancer Registry database. In some cases, we suspect that a patient may have a genetic syndrome that has led to the development of pancreas cancer. In these cases, our genetic counsellors provide information to the patient and his/her family about the syndrome and make referrals for genetic testing when indicated.

One of the ways to identify FPC genes is through the use of genome sequencing (looking at the order of a person's DNA) using powerful machines at the Ontario Institute for Cancer Research (OICR). To date, we have sequenced the entire human genome of 15 people from 7 high risk families, and our students and technicians are combing through the large amounts of data to find the 'needle-in-the-haystack' FPC gene(s). We also sent DNA samples from 75 FPC families to collaborators in Edinburgh, Scotland, to help conduct some of this labour-intensive work.

Identifying the FPC genes is critical in our efforts to detect pancreas cancer in its earliest stages. Once these genes are identified, we will be able to identify the abnormal genetic and protein pathways that are important during the earliest stages of pancreas cancer, devise new treatment strategies, and develop effective screening programs.

This work has been supported through funds from Pancreatic Cancer Canada and the Weston Garfield Foundation.

BRCA MUTATIONS IN PANCREAS CANCER

Mutations (changes) in the BRCA1 and BRCA2 genes can sometimes be found in individuals with pancreas cancer. Typically the BRCA1 and BRCA2 genes cause women to have an increased chance of developing breast and/or ovarian cancer and men to have a higher risk for male breast cancer and/or prostate cancer. Both men and women with BRCA1 or BRCA2 mutations have an increased risk (~5% lifetime although this estimate is still not precise) of developing pancreas cancer. Identifying individuals

with BRCA mutations will have significant impacts on cancer screening, such as increased mammography and breast MRI.

Preliminary research has also shown that individuals with pancreas cancer and a BRCA mutation may benefit from certain types of chemotherapy (e.g. cisplatin) that aren't typically recommended during standard pancreas cancer treatment.

Genetic testing is available for BRCA1 and BRCA2 and some families may be eligible to have this testing depending on their personal and family history of cancer. Families with BRCA mutations tend to have several family members diagnosed with breast, ovarian, prostate and/or pancreas cancer, cancer diagnoses may be at young ages (under age 50), several generations may have these cancers and some individuals may have more than one type of cancer.

Families of Ashkenazi Jewish descent also have a somewhat higher chance of carrying a BRCA mutation. If your family meets these criteria, you may want to have your family history assessed by a cancer genetics clinic. Even if your family history meets some of these criteria, not all individuals will be eligible for genetic testing.

PANCREATIC CANCER GENETIC EPIDEMIOLOGY CONSORTIUM

Our registry is collaborating with several other pancreas cancer registries in North America on a genetic study called PACGENE (Pancreatic Cancer Genetic Epidemiology). The other registries include:

- Mayo Clinic (Rochester, Minnesota)
- Johns Hopkins University (Baltimore, Maryland)
- Karmanos Cancer Institute (Detroit, Michigan)
- MD Anderson Cancer Center (Houston, Texas)
- Dana-Farber Cancer Institute (Boston, Massachusetts)

The goal of this study is to learn about the genetic and environmental causes of pancreas cancer. This information will be used to develop better prevention strategies, and will help us better understand the biology of pancreas cancer and its effective treatments. So far, our centre has enrolled over 400 families across Canada for this research, and recruitment continues.

How Can My Family Participate?

Any family with two or more biologically-related family members diagnosed with pancreatic adenocarcinoma is welcome to contact our registry. We recruit families where the cases of pancreas cancer are living and/or deceased.

What Does Participation Involve?

All participants are asked to complete questionnaires asking about lifestyle and various environmental risk factors, in addition to the family history of cancer. We also ask participants to provide a blood or saliva sample and/or permission for us to obtain a stored tissue sample (from previous surgical procedures) for genetic studies. The most helpful samples are from relatives who have the disease.

We obtain the medical records (where possible) for each diagnosis of cancer in the family. We are interested in enrolling people with the disease as well as their healthy relatives.

All participants have an opportunity to speak with a genetic counsellor about their family history and details of the research. Participation in this study does not require a trip to Toronto. All of your information will remain confidential. If you are interested in participating, please e-mail fgicr@mtsinai.on.ca or call toll free at 1-877-586-1559 and leave a message.

WHAT'S NEW IN THE LAB

Dr. Zaheer Kanji is one of the newest members in Dr. Steven Gallinger's laboratory at the Samuel Lunenfeld Research Institute (SLRI) of Mount Sinai Hospital. He is a third year General Surgery Resident from the University of British Columbia undertaking graduate studies at the University of Toronto over the next couple of years. His goal is to specialize in liver and pancreas surgery and to train in cancer genetics research.

He is studying the development of FPC, looking specifically at the genetic changes that lead to this disease. The OPCS houses one of the largest pancreas cancer databases in the world making it the ideal place to study this devastating illness.

His project examines the DNA from pancreas cancer tumours looking specifically at areas where key cancer preventing genes have been deleted or lost. This will be performed with complex high resolution DNA microchips modelled after the human genome project. Areas of loss may highlight major players in disease causation and lead to the creation of new genetic tests or anti-cancer therapies in the future.

Exome Sequencing Identifies Non-Segregating ATM and PALB2 Mutations in FPC (scientific paper submitted in 2012)

The ATM gene causes ataxia-telangiectasia, also referred to as Louis-Bar syndrome, and is a rare, neurodegenerative, inherited disease causing severe disabilities. PALB2 is a breast cancer susceptibility gene. Recently, there have been claims that mutations in the ATM and PALB2 genes have been associated with FPC.

We used a cutting-edge technology, exome sequencing, to analyze DNA from 48 FPC families and discovered new ATM and PALB2 mutations. These mutations were absent from a relative with pancreas cancer in both families. This challenges whether ATM and PALB2 mutations are high-risk for FPC, and suggests stronger evidence is needed before these genes are routinely sequenced in the clinic.

Genetic Changes Associated with Cigarette Smoking and Pancreas Cancer Risk (scientific paper published in 2012)

Cigarette smoking is an established cancer risk factor. However, given that persons may have different abilities to metabolize carcinogens found in cigarette smoke, we hypothesized that a

person's personal smoking history (for example, never smoker, former smoker, or current smoker) and their genes encode enzymes that break down cigarette carcinogens and work together to influence a person's pancreas cancer risk.

Using data collected from participants of the OPCS, we found that current smokers had more than twice an increased risk for developing pancreas cancer compared to people who never smoked. Individuals that smoked the greatest number of cigarettes for the longest duration were also more likely to develop pancreas cancer.

On the genetic side of things, we found that individuals with certain genotypes for genes encoding enzymes, such as CYP1B1 and UGT1A7, had a lower risk of developing pancreas cancer while individuals with certain genotypes for genes encoding enzymes such as GSTM1 had higher risk.

Finally, we found that cigarette smoking and genotypes of certain enzymes work together to increase pancreas cancer risk. Specifically, we found that smokers with certain genotypes of the enzyme EPHX1 and NAT2 had higher risk for pancreas cancer.

Our study shows that smoking increases pancreas cancer risk, and the genes we carry may modify this risk. The results of our study provide a better understanding of pancreas cancer development, and may also direct future therapies targeting genes. However, more studies looking into these genes are needed to determine whether they play a key role in pancreas cancer development.

While we cannot do anything to change our genetic makeup, we can do something about our smoking status. If you don't smoke – don't start; if you smoke – quit; if you quit – keep up the good work and stay smoke-free!

PAST NEWSLETTERS

For more information about our research, please refer to previous volumes of this newsletter, which may be requested by contacting us and can also be found on our website: www.zanecohencentre.ca/gi-cancers/diseases/pancreatic-cancer/ontario-pancreas-cancer-study-newsletters.

KEEP US INFORMED

Please keep us informed of any changes in your family history of cancer or other conditions. We are interested in this information for all blood relatives in the family. If you are participating on behalf of someone with pancreas cancer, please update us with changes to his/her family history. It is helpful to track this information for research purposes, but it is also important in our assessment of the family history and can help guide clinical recommendations for family members. Please also notify us with changes to your contact information.

If there are any changes, please leave us a message at 1-877-586-1559 or contact your genetic counsellor directly.

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