NETWORK

MOUNT SINAI HOSPITAL

Familial Gastrointestinal Cancer Registry

Volume VII, Issue I Spring 2006

RESEARCH UPDATE

Recent News on Penetrance in HNPCC

Robert Gryfe, MD Department of Surgery

Hereditary Nonpolyposis Colorectal Cancer (HNPCC) is an autosomal dominant disease. This means that children of those affected by HNPCC have a 50% chance of inheriting the genetic mutation that leads to this disease. Those who inherit a genetic mutation that leads to HNPCC are known as carriers. However, not all carriers of a genetic mutation that cause HNPCC will develop colorectal (or any other) cancer. The risk of a carrier developing cancer is known as *penetrance*. Historically, HNPCC is believed to have a penetrance of approximately 80% and an average age of colorectal cancer diagnosis of 44 years. Calculating the likelihood of being affected with cancer, the type of cancer and the age of cancer diagnosis are all important in developing rational clinical screening programs for those at risk of developing HNPCC cancers.

Despite the fact that HNPCC has been described as a colon cancer syndrome, numerous other cancers are observed in HNPCC families. These include *endometrial* (womb), small bowel, *ureter* and many other cancers. In 1997, Dr. Malcolm Dunlop examined a number of Scottish HNPCC families and observed that women with HNPCC were in fact at greater risk for developing endometrial cancer —42% lifetime risk, compared to developing colorectal cancer —lifetime risk 30%. Men on the other hand appeared to have a 74% lifetime risk of developing colorectal cancer. Thus, it appears that at least in women with HNPCC, endometrial cancer may be more commonly diagnosed than colorectal cancer.

Recent analyses by our colleagues in Australia suggest that we have probably overestimated penetrance in HNPCC. This means that the lifetime risk of colorectal cancer in gene carriers may be around 35-45%, not nearly as high as original estimates.

In summary, recent publications suggest:

1. Previous HNPCC penetrance estimates of 80% are more likely to be in the 40-50% range.
2. The risk of endometrial cancer may be as great (or greater) than that for colorectal cancer in female HNPCC mutation carriers.
3. The average age of colorectal cancer in HNPCC is between 45-55 years.

While it appears that an 80% lifetime risk of colorectal cancer with an average age of diagnosis of 44 years in HNPCC may be an overestimate, more research in this area is necessary before individually tailored changes in clinical recommendations can be made.

NEWSFLASH

Familial Colorectal Cancer Type X – A New Syndrome?

by Steven Gallinger, MD, MSc, FRCSC, Director, Familial GI Cancer Registry

It is well known that someone with a family history of colorectal cancer has a greater risk of developing colorectal cancer themselves. There are different forms of hereditary colorectal cancer and researchers are analyzing these families to calculate more accurate estimates of colorectal cancer (and other) risks. Hereditary Nonpolyposis Colorectal Cancer (HNPCC) is a condition where tumors show a specific genetic abnormality called *microsatellite instability* which is caused by mutations in genes called *mismatch repair genes* (or MMRs). People with MMR mutations are at increased risk of colorectal cancer, and they are also at higher risk for cancer of the uterus, stomach, ovary, and ureter (and possibly others). Until recently, it was believed that this high risk was present in ALL families with striking family histories (called *Amsterdam criteria family* histories, based on the definition of HNPCC at a conference in Amsterdam in 1991). Using detailed family histories collected from individuals in Canada, the United States, and Australia (data from our local Familial Gastrointestinal Cancer Registry at Mount Sinai Hospital, and our Ontario Familial Colorectal Cancer Registry at Cancer Care Ontario were included in this study), a new report suggests that individuals from Amsterdam criteria families ***without*** MMR mutations are at much lower risk of colorectal cancer, and other cancers, compared to people from Amsterdam criteria families ***with*** MMR mutations. In this paper by Lindor et al, over 150 high risk families, containing over 3,400 relatives were analysed. The main results are highlighted below.

…"a new report suggests that individuals from Amsterdam criteria families* without *MMR mutations are at much lower risk"…

Cancer Type	Risk in Families with MMR mutations	Risk in Families without MMR mutations
Colorectal	4-10 times higher than normal population	2-3 times higher than normal population
Uterus	3-5 times higher than normal population	same risk as normal population
Stomach	3-7 times higher than normal population	same risk as normal population
Breast	same risk as normal population	same risk as normal population
Ovary	2-3 times higher than normal population	same risk as normal population
Prostate	same risk as normal population	same risk as normal population
Ureter	6-10 times higher than normal population	same risk as normal population
Lung	same risk as normal population	same risk as normal population

Continued on page3

NEWSFLASH *Continued from page 2*

Since these differences are so striking, it has been suggested that high risk colorectal cancer families ***without*** MMR mutations be called Familial Colorectal Cancer Type X, to distinguish them from HNPCC caused by MMR mutations.

Genetic clinics will use this new finding to help tailor colorectal cancer screening strategies to more accurately reflect the degree of increased risk associated with the various syndromes.

Lindor et al., JAMA. 2005 Apr 27;293(16):1979-85

CLINICAL FOCUS

INTERVENTIONAL ENDOSCOPY

Paul Kortan, MD
Dept. of Gastroenterology St. Michael's Hospital Toronto, ON

Many of our readers with Familial Adenomatous Polyposis (FAP) are aware of the need for regular examination of the first part of the small intestine where *polyps* may develop. The question about how to treat duodenal polyps is often asked. Read about what is new in this field as described by a specialist in gastroenterology.

Q **My gastroenterologist says I need to be referred to a specialist in interventional endoscopy because I have duodenal polyps. What is the difference between my regular scope and interventional endoscopy?**

A Regular endoscopy is a diagnostic technique that allows viewing of your *duodenum* to diagnose or biopsy duodenal polyps while at interventional endoscopy, the polyp is actually removed or destroyed.

Q **I have duodenal polyps which my gastroenterologist says can be removed with endoscopic resection. Is this the same thing as duodenal surgery?**

A No. Endoscopic resection of polyps is performed under conscious sedation usually on an out-patient basis. The endoscope is introduced into your duodenum through your mouth and the polyp is removed with a special device called a snare with the help of electrical current.

Q **I have a large polyp in the duodenum around the opening of the bile duct and pancreas and was told I need to have an ampullectomy. Does this always require surgery?**

A No. Ampullectomy can be performed surgically or endoscopically. The choice of treatment depends on the size and appearance of the ampullary polyp. Smaller polyps are removed with interventional endoscopy, large polyps usually require surgery.

Q **I have many large polyps in the opening of my stomach which my doctor called the antrum. Can polyps be removed by burning them out? Do you still biopsy them?**

A Polyps in the antrum are usually first biopsied to find out what kind of polyps they are. If they have a pre-malignant potential, they are usually removed endoscopically by burning them off.

Q **I take Aspirin from time to time. Do I have to stop this medication before a procedure? What about after?**

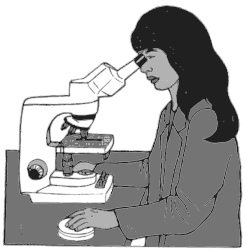
Continued on page 5

MEDICAL NEWSFRONT

Familial Adenomatous Polyposis (FAP) and Desmoid Disease

by Carol A. Durno, MD, MSc, Registry Pediatric Gastroenterologist

Desmoid disease is a growth or a tumour that can develop in people with Familial Adenomatous Polyposis (FAP). Desmoid tumours also occur in people who do not have FAP. Overall approximately 10% of people with FAP develop desmoids. Desmoid tumours are not cancers. Even though the tumour is not malignant (cancerous), desmoids can be serious. The majority of these tumours arise in the abdomen either within the wall of the abdomen or inside the lining of the abdomen around the intestines. Less often desmoids can develop on the trunk or limbs (legs and arms) or breast. Desmoids may cause no symptoms. They can cause symptoms by pushing on structures such as the intestine or ureters (tubes that drain the kidneys). Patients may notice a swelling in the abdomen or may develop abdominal pain and/or vomiting. These tumours are often very slow growing. Desmoids do not hurt to touch and usually feel quite firm. Patients should contact their doctor or surgeon if they are concerned about any symptoms or growths. Patients are usually evaluated for desmoids by a physical examination and imaging such as an ultrasound, CAT scan or MRI.



Among patients with FAP, a desmoid may be diagnosed prior to, simultaneously, or after the diagnosis of FAP. Certain factors cause an increased risk of developing desmoids. A family history of desmoid disease makes developing a desmoid more likely in that individual. A number of specific mutations (genetic changes) that cause FAP also are associated with desmoid disease. FAP-associated desmoids have been linked to trauma, particularly colectomy (removal of the colon). There is no good evidence to suggest that the type or extent of surgery influences desmoid development. We are conducting a study to see if removal of the colon earlier in life increases the chance of developing a desmoid. This will have significance for patients with a family history of desmoid because of the timing of the surgery in young adulthood.

Treatment of desmoids varies depending on the location of the desmoid, that is, within or outside the abdomen, and the size of the tumour. We know that operating on desmoids that are present within the lining of the abdomen may result in their return and in their growth. Medication is the main approach for desmoids within the lining of the abdomen while surgery may be recommended for a desmoid in the wall of the abdomen. Medications include nonsteroidal anti-inflammatory drugs (like sulindac), anti-estrogens (like Tamoxifen), and chemotherapy for aggressive desmoid disease. Currently multi-centre studies are being developed to look more closely at the different treatments to determine what is the most effective.

> ***"Treatment of desmoids varies depending on the location of the desmoid"…***

There are many quality of life issues for patients with desmoid and for their families. In a recent questionnaire sent to our Registry patients, the following problems were highlighted: concern about the lack of knowledge among health professionals; changes in awareness of appearance; feelings of loss and uncertainty; concern for family; and coping strategies.

Please see Volume V, Issue 1 of "Network" for the full article, either on line:www.mtsinai.on.ca/familialgicancer or on request to the Registry.

Clinical Focus *(continued from page 3)*

A If the procedure is diagnostic with or without biopsies, you may remain on Aspirin before and after the procedure. If the procedure is interventional with intention to remove gastric and duodenal polyps, Aspirin should be discontinued 10 days before the procedure and may be re-started one week after the procedure. However the decision to discontinue Aspirin may be individualized and will be discussed with your physician.

Q **Why do I have to have bloodwork done before a procedure? What kind of bloodwork is required?**

A Because there is a small risk of bleeding following removal of polyps, it is important to assure that your hemoglobin and clotting of the blood, as well as kidney and liver function, are normal.

Q **Normally, I do not eat or drink for 8 hours before a gastroscopy. Is the preparation the same?**

A Yes.

Q **Will I receive the same kind of sedation?**

A Yes, you will receive conscious sedation that is used for diagnostic and interventional endoscopy.

Q **Is this an out-patient procedure or will I have to stay in hospital afterwards?**

A It depends on the size and number of polyps. For smaller polyps, this is an out-patient procedure unless there is a complication. For large polyps or polyps of *ampulla*, you are usually hospitalized for 2 days.

Q **Will I be able to go to work the next day?**

A If the procedure was performed on an out-patient basis and you feel well, you may return to work the next day.

Q **How can I find a gastroenterologist who does interventional endoscopy?**

A Discuss it with your physician who will refer you to a centre with expertise in interventional endoscopy.

New Study

Study Participants Needed

Study Title: Addressing the Quality of Life of Patients and Families Obtaining Genetic Services

Purpose: The aim of the study is to developing a new "clinical tool" for physicians and genetic counselors to assist them in assessing adjustment and support needs of individuals using genetic services.

Who is Eligible:

1. Individuals going through genetic testing/counseling for Cancer
2. Fluency in English
3. 18 years or older

Individuals who participate in this study, will be asked to complete a brief set of questionnaires on well-being and perceptions of undergoing genetic testing; and may receive a brief follow-up telephone interview. The questionnaires will be repeated at two time-points and will take less than 30 minutes to complete.

If you are interested in learning more about this study, please contact the study coordinator, Nicole Taylor at (416) 340-4800 Ext. 6905, or the Principal Investigator, Dr. Mary Jane Esplen at (416) 340-3024, or ask your genetic counselor for more information.

EDITOR'S MAILBAG

Q I look just like my mother, and take after her in many ways. She has had colon cancer. Does that mean I'm likely to get it too?

A Not necessarily. Half of our *genes* come from our mother, and half from our father. Our genetic make-up is therefore a unique combination of traits from each of our parents. Our genes determine what we look like, how we grow and develop, and also some diseases we might be susceptible to. However, if we take after one parent for a certain physical trait, like height or eye colour, we cannot assume that we also take after them in other ways, such as predicting for which medical conditions we might be at risk. Except in families where there is a known hereditary cause for colorectal cancer, such as Familial Adenomatous Polyposis (FAP) or Hereditary Non-Polyposis Colorectal Cancer (HNPCC), cancer risk is probably determined by a combination of things. Besides genetics, other factors that might contribute to cancer predisposition might be diet, lifestyle and environmental exposures. We still have a lot to learn about the causes for colorectal cancer, and cancer in general.

Q My family has been told that we are not eligible for genetic testing, but am I still at higher risk for colorectal cancer?

A If you have a family history of colorectal cancer or polyps, then yes, your risk for colorectal cancer will likely be higher than the general population. Since colorectal cancer is a relatively common type of cancer, it is not unusual to have a family history of this disease. However, hereditary colorectal cancer affects only about 5-10% of patients with colorectal cancer. So not all families affected by colorectal cancer will be at risk for hereditary cancer. Even when genetic testing is not indicated, we cannot ignore a family history of cancer. The risk for relatives depends on the number of family members with the disease, how closely they are related, and their ages of diagnoses. Anyone with any relative diagnosed with colorectal cancer should review the family history with their physician to discuss what screening recommendations are appropriate for them. In most cases, we recommend screening colonoscopy around the age of 40 for people who have a family history of polyps or cancer, or 10 years younger than the youngest case, whichever is earlier.

Q If my family is at risk for hereditary cancer, but we do not really wish to pursue genetic testing, is a genetic counselling appointment still available to us?

A Yes. A genetic counselling appointment does not always require that a family will be eligible for, or interested in, genetic testing. Genetic counselling involves a discussion about the chance of hereditary cancer and the risks

Continued on next page

Editor's Mailbag *(continued from page 6)*

for cancer for family members. Most importantly, we can also discuss the appropriate clinical screening recommendations for family members (eg. who should have a colonoscopy, at what age should screening begin, and how often) based on the cancer diagnoses in the family. There is also discussion about other types of cancer for which the family could be at risk for. Often, families may have other questions or concerns about the family history and hereditary cancer and this would be a good opportunity to discuss.

Q I don't like the prep before having a colonoscopy, and I have heard that there is a virtual colonoscopy. What is a virtual colonoscopy and how is it different from a conventional colonoscopy?

A A virtual colonoscopy is similar to a conventional colonoscopy in that it is a screening tool used to look for bowel diseases, such as colorectal cancer. A virtual colonoscopy uses MRI or CT scans along with computers to produce images of your colon. Like a conventional colonoscopy, a virtual colonoscopy still requires that you remove all the stool from your colon before the procedure. During a virtual colonoscopy a small tube is inserted into the rectum and the colon is inflated with air; this allows better visualization of the colon. A MRI or CT scan is then used to produce a series of pictures of the colon. These pictures are then processed by a computer to create the computer image of the colon. A virtual colonoscopy can be more comfortable for some people since a conventional colonoscope is not used. However, a virtual colonoscopy does NOT allow the physician to take biopsies or remove any polyps. If polyps are found, you will have to return for a conventional colonoscopy. We consider conventional colonoscopy the "gold standard" and recommend it as the preferred screening method. Virtual colonoscopy is still considered an investigational procedure in Ontario.

Registry Update

InSiGHT

by Kara Smith, MSc, (C)CGC

The first conference of the International Society for Gastrointestinal Hereditary Tumours (InSiGHT) met in Newcastle Upon Tyne, UK in June 2005. InSiGHT is a new organization formed by the merger of two preexisting networks for FAP and HNPCC. Members of InSiGHT include clinical and research groups from all over the world, whose primary interest is inherited colorectal cancer. There were representatives from groups in Canada, United States, Europe, Australia, South America, Israel, Korea, Japan, China,.

There are many countries that have colorectal cancer registries similar to ours. The purpose of the international meeting is for the different groups to share their current research findings and to brainstorm ideas for future research. The meeting also provides the opportunity for collaborative research between centres. Since the research findings have direct clinical implications, there was also much discussion about how to improve the care for patients and families with hereditary colorectal cancer.

Being part of this international organization allows for unlimited possibilities for furthering our knowledge about hereditary colorectal cancer. We look forward to the next InSiGHT meeting scheduled for March 2007 in Yokohama City, Japan.

Network

A publication of the
Familial Gastrointestinal Cancer Registry
Mount Sinai Hospital
Suite 1157
600 University Avenue
Toronto, Ontario, Canada
M5G 1X5
Editor:
Terri Berk
Clinical Co-ordinator

If you would like to know more about inherited bowel diseases, please write or call us

Phone: 416-586-4800
ext. 8334
e-mail: tberk@mtsinai.on.ca
www.mtsinai.on.ca/familialgicancer

MOUNT SINAI HOSPITAL

Glossary

Ampulla: Enlargement of the ducts from the liver and pancreas at the point where they enter the small intestine.

Amsterdam Criteria Families: Families with all of the following features:

1. Three relatives diagnosed with HNPCC related cancers/lesions
2. One of these relatives is a first-degree relative of the other two
3. Diagnosed relatives span two successive generations
4. One case of cancer is under the age of 50

Duodenum: The first part of the small intestine, extending from the pylorus (bottom part of the stomach) to the jejunum (second part of the small intestine).

Endometrial cancer: Refers to cancer in the lining of the uterus. Also commonly called uterine cancer.

Gene: A specific unit of DNA which contains instructions for the body to grow, develop and function.

Microsatellite instability: A tumour characteristic that is observed in 15% for all colorectal cancers. This is very common in tumours from individuals who have HNPCC.

Mismatch repair genes: Genes that detect and repair "spelling" mistakes that occur during DNA replication.

Penetrance: The risk of developing a disease given you carry the genetic mutation.

Polyp: Excess tissue that grows inside the body. There are many different types of polyps; some types, such adenomas have a higher potential to become cancerous.

Ureter: The collecting tube that carries urine from the kidney to the bladder.