MOUNT SINAI HOSPITAL
Joseph and Wolf Lebovic Health Complex
Zane Cohen Centre for Digestive Diseases

NETWORK
Familial Gastrointestinal Cancer Registry

A patient care, teaching and research centre affiliated with University of Toronto **Summer 2011**

CLINICAL FOCUS

Surveillance colonoscopy for polyps in adolescents: Why is everyone at risk not being appropriately screened?

Dr. Carol Durno, MD, MSc
Pediatric Gastroenterologist

Colon cancer has been reported in teenagers. Patients with conditions such as Familial Adenomatous Polyposis (FAP) and Juvenile Polyposis Syndrome (JPS) are at increased risk for colon cancer. Studies show that colonoscopy does save lives and decreases the risk of developing colon cancer. As a pediatric gastroenterologist, my goal is to help all teenagers who are at risk of developing polyps and colon cancer to feel empowered. You can look after your own health and feel like you have control over your body so you have a healthy life.

In order to successfully implement effective cancer screening programs for teenagers, it is important to understand the concerns of adolescents and parents. Knowing the reasons that encourage or discourage surveillance colonoscopy in adolescents will better equip health-care professionals helping teenagers. There are many reasons why some teenagers do not follow surveillance recommendations.

I have met teenagers who had bad endoscopy experiences such as not receiving enough, or any, sedation for examinations. They report feeling "invaded". Others teens describe hearing stories from their parents when they had a painful experience years ago with colonoscopy, leaving the teenager afraid to have a procedure. We would like to ensure teenagers have positive experiences with surveillance so that high compliance rates into adulthood will be maintained.

Compliance means following the recommended screening protocol such as yearly colonoscopy.

Teenagers often feel like they have more control over their bodies when they can make choices. Some teenagers like to be able to decide what time of year to have endoscopy so it does not interfere with specific sports teams or school. Many teenagers are "freaked out" or "scared" about a very specific part of the procedure such as having the intravenous (**IV**) started. They relate feeling less anxious if they can have gas sedation and have the IV inserted once they are asleep.

Some patients have a difficult time emotionally returning to the hospital for scopes after bowel surgery, as being at the hospital brings back memories of their operation. Many teenagers tell me they feel "angry" or "sad" or "feel different" from their friends. Parents report that they feel like they are constantly nagging their son/daughter about the need for surveillance and this conflict only makes the teenager more upset. There are people such as social workers who have special training and can provide support to teenagers to help deal with difficult feelings. There are lots of people who want to help make you feel better. The majority (85%) of our Registry patients who participated in a recent quality of life study after having a **colectomy** (operation to remove the large bowel or colon) before 15 years of age for FAP reported compliance with their scopes. Seventy percent intended to continue with surveillance.

Patients who comply with surveillance listed reasons for continuing surveillance as, "my doctor recommends surveillance;" "to decrease my worry of developing colon cancer;" "to increase chances of better recovery if polyps are detected; " and "to take care and control of my body".

Some groups have used written and telephone contacts designed to promote compliance. This system resulted in

twice as many patients keeping to their scheduled scope. Perhaps teenagers would prefer email or text reminders to schedule appointments. We would like to hear from you. Tell us about your endoscopy experiences. What approaches do you feel would help increase compliance? For contact information, please go to page 6.

RESEARCH CORNER

The Search for the Genetic Basis of Familial Colorectal Type X

Dr. Steven Gallinger, MD, MSc, FRCSC
Registry Co-Director

Colorectal cancer remains a major health problem among Canadians with over 9,000 deaths from this malignancy projected in 2010. Although mass screening of the general population has become a reality in most provinces, many public health challenges remain including: limitations of currently available stool-based screening kits; poor compliance of the population for mass screening; inadequate capacity of the healthcare system for follow-up colonoscopy of a positive screen test; and the need for targeted screening of high-risk groups.

It is the high-risk groups, patients strongly predisposed to develop colorectal cancer, where aggressive screening is likely to have the greatest impact. In fact, at least 20% of all colorectal cancer cases appear to have a significant family history of **adenomatous** (precancerous) polyps and/or colorectal cancer.

The past twenty years of research in the genetics of colorectal cancer have resulted in the characterisation of three high-risk genetic syndromes: Familial Adenomatous Polyposis (FAP), Lynch syndrome (LS) or Hereditary Nonpolyposis Colorectal Cancer, and MYH Associated Polyposis (MAP).

Since these syndromes account for at most 3-4% of hereditary colorectal cancer, it is now well accepted that a large fraction of hereditary colorectal cancer, recently defined as Familial Colorectal Cancer Type X (FCTX), should be studied in greater depth.

Moreover, the recent advent of novel and affordable tools to sequence the **genome**, provides an exciting opportunity to take advantage of many years of recruitment of FCCTX families into Canadian high-risk registries to identify the genetic basis of this syndrome. FCCTX is defined as families with multiple cases of colorectal cancer, which satisfy the Amsterdam Criteria

1. at least three relatives with confirmed colorectal cancer, one of whom is a first-degree relative of the other two; FAP should be excluded;

2. at least two successive generations involved;

3. at least one of the cancers diagnosed before age 50),

describing very high-risk families, and where there is no evidence of DNA **mismatch repair deficiency** which is the hallmark of Lynch syndrome.

Together with colleagues at the Ontario Institute for Cancer Research and at Memorial University in Newfoundland, we have recently been awarded a three-year Canadian Cancer Society Research Initiative grant to use **exome sequencing** to identify **genetic variants** in Canadian FCCTX families. The families were recruited by the Familial GI Cancer Registry at Mount Sinai Hospital, the Ontario Familial Colorectal Cancer Registry, and the Newfoundland Familial Colorectal Cancer Registry.

Using sophisticated and cost-effective DNA sequencing technology, we will search for new genes that cause FCCTX. Once identified, we will contact research groups worldwide who are conducting similar studies and confirm that these new genes cause FCCTX in other high-risk families. The identification of these genes opens up many new research avenues in understanding the biologic mechanisms that cause colorectal cancer and unique opportunities for targeted cancer prevention through effective colonoscopic screening.

REGISTRY UPDATE

Gynecological Cancers: Managing the Risks

Eriskay Liston, MS, CGC
Genetic Counsellor

We know that having Lynch syndrome (LS) is associated with a significant risk for endometrial cancer, as well as an increased risk for ovarian cancer.

However, unlike colorectal cancer screening, to date, gynaecologic cancer screening has not been shown to be very reliable in the detection of ovarian or **endometrial** (lining of the womb) cancer. Currently the National Comprehensive Cancer Network advises that individuals with LS be referred to a gynaecologic oncologist for gynaecologic cancer screening, which can include: an annual **transvaginal ultrasound**, uterine biopsy, and a blood test measuring **CA-125**.

Unfortunately there is a lack of evidence supporting the effectiveness of screening for either endometrial or ovarian cancer. Since the benefits of screening for gynaecologic cancers are largely unknown, we counsel women with LS to be able to recognize the symptoms of endometrial cancer and advise them to speak to their family doctor or, other medical professional, right away if symptoms present.

Symptoms to be concerned about are: any abnormal vaginal bleeding such as bleeding between periods, heavy periods/clots or prolonged periods or any vaginal bleeding after menopause. Knowing these symptoms and speaking to your doctor about a referral to a gynaecologic oncologist is very important and may be the most effective way to detect endometrial cancer at an early stage.

Having these symptoms does not necessarily mean that an individual has cancer; it just means that a specialist should investigate the cause of such symptoms. We also recommend discussing the option of taking oral contraceptives with your doctor since this has been linked to a reduced risk for ovarian cancer.

Another risk-reducing option for women with LS is the possibility of having **prophylactic** surgery to remove their uterus, fallopian tubes, and ovaries. There are no set recommendations at this time for women with LS regarding this type of surgery; however, it is thought that prophylactic surgery is a reasonable option for significantly reducing the risk of developing endometrial and/or ovarian cancer. We highly recommend a thorough discussion with a gynaecologic oncologist regarding the risks and benefits of this kind of surgery, as each person may have specific concerns unique to their situation.

If you, or any of your family members, have questions or would like to discuss this information further, please contact your genetic counsellor with the contact information on page 6.

Research Project: Managing the Risks of Gynecological Cancer Associated with Lynch Syndrome

Dr. Tae Hart, PhD
Associate Scientific Staff

Dr. Tae Hart, together with genetic counsellors Melyssa Aronson, Spring Holter, and Eriskay Liston and her graduate student Lindsay Torbit, is beginning a new research project to examine women's ability to manage their gynaecological risk associated with Lynch syndrome. Although Lynch syndrome is known to increase the risk of developing gynaecological cancer, such as endometrial or ovarian cancer, very little information exists with regard to how women feel about managing their cancer risk.

Specifically, we will be examining the kinds of screening and risk reduction steps that women personally engage in. We will also be looking at women's preferences for being involved in their own medical care, their perceptions about having Lynch syndrome, and their beliefs about how well their family doctors are managing their Lynch syndrome related gynaecological cancer risks.

We will be contacting women who are part of the Familial GI Cancer Registry and requesting that they complete a packet of questionnaires. Our ultimate goal is to gain a better understanding of how women with Lynch syndrome feel about managing their gynaecological cancer risks and to gain insight into how to improve their interactions with the medical system.

RESEARCH UPDATE

Pregnancy after Gastrectomy in Women with Hereditary Diffuse Gastric Cancer Syndrome

Melyssa Aronson, MS, CGC
Senior Genetic Counsellor

Individuals who find out they have an inherited stomach cancer condition known as hereditary diffuse gastric cancer syndrome (HDGC) have a difficult decision to make. Since it is so challenging to detect stomach cancer, carriers of HDGC often decide to remove their stomach in order to eliminate their risk of developing stomach cancer. This surgery is called a prophylactic total **gastrectomy**, which means elective surgery to remove the entire stomach.

The Zane Cohen Centre has been dedicated to offer complete support to individuals contemplating this decision through our expert surgeons, genetic counsellor, nutritionist, pharmacologist, pathologist and psychologist. We are also leading the first Canadian study to help understand the impact of this type of surgery on HDGC patients.

We are often asked whether pregnancy after a prophylactic total gastrectomy is possible, as this surgery is often done when women are still in their child-bearing years. A study came out in the 2010 journal **Familial Cancer** (9:331-334) that looked into this question.

Some of you may recognize the head author of this study, Pardeep Kaurah, as she worked in our Registry as a genetic counsellor before moving to the British Columbia Cancer Agency where she is pursuing her PhD.

The study followed four women who had seven babies following their gastrectomy. The main complication seen was pregnancy-induced **anemia** (low red blood count), due to difficulty in absorbing certain nutrients such as vitamins B12 and D, calcium, folate, and iron. The anemia resulted in a blood transfusion for one mom, and iron and vitamin supplements for the others. The seven pregnancies resulted in healthy babies for these four women.

There were two other British studies that looked at 138 women who had gastrectomies for reasons other than cancer. No issues were reported in the woman's ability to become pregnant or deliver the baby, although anemia was observed in many of the mothers during the pregnancy.

While this is a very small study, pregnancy and healthy babies are possible for women with HDGC who undergo a prophylactic total gastrectomy. The study recommends women considering pregnancy after their surgery consult a nutritionist throughout the pregnancy and be monitored by an obstetrician. Women should take vitamins prior to pregnancy to avoid beginning the pregnancy with nutrient deficiencies.

NEWSFLASH

A recent meeting was held by the International Society for Gastrointestinal Hereditary Tumours in San Antonio, Texas, attended by 178 specialists with expertise in inherited colorectal cancer.

This gathering, every two years, allows for the sharing of new medical and scientific information. Through member Registries, we are able to improve the treatment and care for affected patients and their families affected with rare disorders such as FAP, attenuated FAP, juvenile polyposis syndrome, Peutz-Jeghers syndrome, Lynch syndrome, hereditary gastric cancer and hereditary pancreatic cancer.

The emphasis on early detection and prevention of cancer remains a major focus.

What's New in Colon Cancer Genetics?

Dr. Bharati Bapat, PhD
Molecular Geneticist

There were exciting presentations and vigorous discussions about different genes involved in colorectal cancer and how they cause susceptibility to colorectal, and other associated, cancers. A few highlights are presented below.

Changes in the genetic code or mutations of mismatch repair genes cause Lynch syndrome. However, recent studies have uncovered another route or path adapted by the same genes to cause inherited colorectal cancer. This new mechanism does not involve mutations but rather epimutations.

For example, the mismatch repair gene MLH1 can be "turned off" or "silenced" by a mechanism known as DNA methylation. Usually, MLH1 methylation occurs in tumours of about 15% of patients with colon cancer. MLH1 methylation in tumours is not always associated with a family history of colorectal cancer. However, in a few individuals, MLH1 methylation is seen in the cells obtained from their blood, as well as normal cells obtained from other tissues, including normal colon.

This type of MLH1 methylation, seen in normal cells, is known as "epimutation", and can be passed on to the next generation, similar to inherited mutations. Families carrying such epimutations also belong to Lynch syndrome, with an increased risk of colorectal and endometrial cancer.

Guilt by Association

Genetic mutations of another mismatch repair gene, MSH2, are known to cause Lynch syndrome. EPCAM is a neighbouring gene, which lies right next to MSH2. In some Lynch syndrome families, it is the EPCAM gene that is partially deleted in normal blood and tissue cells. Interestingly, the deletions of the EPCAM gene affect the MSH2 gene, causing it to be silenced in these patients due to methylation.

Again, EPCAM deletions can be passed onto the next generation and are the underlying culprit in some affected families.

New Kid on the Block

A new gene causing an increased risk of familial colon cancer was reported at this meeting. This gene, PTPRJ, was discovered by examining blood samples from patients with a family history of colon cancer, but without a clinical history of polyposis. A portion of the PTPRJ gene was found to be copied in these patients which again resulted in gene silencing. Such PTPRJ epimutations were passed on to the next generation, thereby causing familial colon cancer.

Studies are now in progress to understand how many patients or families may be affected by this brand new gene. Stay tuned for updates on this exciting development.

What's new at the Zane Cohen Centre for Digestive Diseases?

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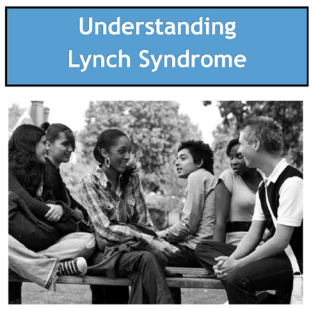

Information for people who may have Lynch syndrome and their family members

TO IMPROVE TREATMENT

We are pleased to announce that after much hard work by our dedicated team at the Zane Cohen Centre for Digestive Diseases, we have published an educational pamphlet on Lynch Syndrome, titled "Understanding Lynch Syndrome". We are excited to be able to give our patients and their family members some reading material that covers all the main points about LS in an easy to follow format.

We hope that it will help people understand the big picture as well as the details that can sometimes be overwhelming when hearing about LS for the first time. We felt that it could also be useful to have the pamphlet on hand to review with family members and even other medical professionals.

The concept of genes and inheritance can be confusing, even for medical professionals, so we have included diagrams that make learning about genetics and LS easier. With an introduction to our centre, we aim for our patients and their families to get to know us, and feel free to contact us with questions at any time.

If you or a member of your family has Lynch syndrome and would like a pamphlet they are available and we would be happy to send you one, just let us know. For contact and website information, please go to page 6.

GLOSSARY

Adenomatous: precancerous polyp.

Anemia: low red blood count

Colectomy: removal of the large bowel.

Exome sequencing: a method of detection for any permanent change in genetic material.

Gastrectomy: removal of the entire stomach.

Gene: a unit of inheritance.

Genome: the full complement of DNA.

CA-125: a protein that can be measured in the blood that is sometimes used to screen a woman for ovarian cancer.

Gynaecologic cancer: cancer that starts in a woman's reproductive system, such as in the womb, also called uterine or endometrial, or in the ovaries.

Gynaecologic oncologist: specialist trained in caring for women at risk for, or with cancers of, their reproductive system.

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

Transvaginal ultrasound: an exam where a wand is inserted into the vagina to look at a woman's reproductive system.

Uterine biopsy: a procedure where a small sample of tissue is taken from the uterus (womb) to examine.

Menopause: the time when a woman permanently stops having her period (usually around 45-55yrs old).

Oral contraceptives: a type of birth control with estrogen and or progesterone (hormones) that is taken in the form of a pill.

Prophylactic surgery: a procedure where surgery is done to remove tissue or organs at risk for cancer, such as the uterus and or the ovaries, before cancer develops.

We Invite You To Partner With Us ...

... as we "join the dots more quickly" to bring new knowledge into practice for better care for patients and their families.

There are many ways to support our work. These include gifts of cash, stocks or existing insurance policies.

Legacy gifts to the Zane Cohen Centre for Digestive Diseases can also be designated in a will.

To donate online
www.zanecohencentre.ca/donate

or contact
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