NETWORK

MOUNT SINAI HOSPITAL

Familial Gastrointestinal Cancer Registry

Winter 2005

Clinical Focus

Vioxx Update

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The class of medications called COX-2 inhibitors (e.g. celecoxib – Celebrex; rofecoxib – Vioxx) were introduced in the 1990s as breakthrough products for the treatment of arthritis and musculoskeletal pain. They are a more selective version of the traditional drugs knows as NSAIDs (non-steroidal anti-inflammatory drugs). Their development arose due to the known serious side effect profile of the traditional NSAIDs (e.g., indomethacin, ibuprofen, naproxen) that included ulceration of the lining of the digestive tract that often resulted in serious problems related to bleeding ulcers.

In addition to the pain-relieving and anti-inflammatory properties of NSAIDs, it was recognized long ago that this class of medications are able to slow and occasionally reverse the growth of colonic polyps. However, their use in this setting was limited by the gastrointestinal side effects. It was eventually recognized that the COX-2 enzyme is present in polyps and may stimulate their growth. Much enthusiasm resulted when the COX-2 inhibitors were discovered as it was felt that these medications would have the potential to decrease polyp growth and help prevent colorectal cancer from developing without the significant side effects of the traditional NSAIDs.

After clinical investigation, Celebrex was approved for use to treat patients with Familial Adenomatous Polyposis (FAP) by the FDA in the US in 1999 and subsequently by Health Canada in 2002. Over the last several years ongoing investigation has been underway to further evaluate Celebrex and also to study the medication Vioxx for use in the setting of FAP as well as in the general population for polyp prevention. In fact, as some of you may be aware, the MSH FGICR had been leading a multi-centre, international study to assess the utility of Vioxx in FAP for polyp prevention.

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On September 30, 2004 Vioxx was withdrawn from the market voluntarily by Merck Frosst, the company that had been manufacturing and distributing Vioxx, and all trials involving the use of Vioxx were halted. This came about due to analysis of data from a study that was underway to test the use of Vioxx to prevent the recurrence of colonic polyps in the general population. An interim analysis suggested that in individuals using 25mg per day of Vioxx continuously for 18 months there was an increased risk of serious cardiovascular events such as heart attack or stroke. The risk appeared to be related to the length of time and the total daily dose individuals were on, however, it was not possible to identify with certainty who would be at risk for such events. It is also not clear at this time why these side effects have occurred but they may be related to a tendency of the drug to promote clotting in blood vessels.

Health Canada, however, has specifically warned that Celebrex should no longer be used in patients with FAP

Several months later information was released regarding Celebrex and Bextra (another COX-2 inhibitor) suggesting that those taking higher doses of these drugs were also experiencing an increased risk of serious cardiovascular events such as heart attack or stroke. Despite those results, at this time, Pfizer (which makes Celebrex and Bextra) has not removed these products from the market but rather asks individuals using them to speak with their physicians. Health Canada, however, has specifically warned that Celebrex should no longer be used in patients with FAP for polyp prevention.

Summary and Current Recommendations:

Despite these potentially worrisome developments individuals who have previously used these products or are currently on them should not panic but rather speak to their own physicians or contact us at the FGICR. Vioxx should no longer be used by any patients and should be discontinued immediately. For those who have participated in the Vioxx study here for FAP, there is very little reason to be worried, however, it is advisable for interested individuals to discuss any concerns with us or with their own family physicians. For those individuals currently using Celebrex for FAP or other conditions to prevent polyp formation, it is advised to discontinue the medication and speak with us or your family physician. Celebrex has not been taken off the market, however, the dose recommended for FAP (400mg twice per day) may contribute to the increased risk of cardiovascular events. Only time and further study will eventually determine whether COX-2 inhibitors will be able to be used safely for those with a high risk of colorectal cancer. We continue to be involved in research to evaluate additional products that may be better and safer for decreasing the risk of colon cancer. ■

Volunteers Needed: New Chemoprevention Study Comparing Aspirin & Starch

CAPP2 (Concerted Action against Polyps) is a prevention study looking at the effectiveness of aspirin and starch in reducing the risk of developing polyps and colorectal cancer. It is an international collaborative study in which Mount Sinai is participating. Individuals who are eligible include those who carry a mutation in one of the genes (*MLH1, MSH2, MSH6*) that causes Hereditary Non-Polyposis Colorectal Cancer (HNPCC), or individuals who have had colorectal cancer and have a family history suggestive of HNPCC.

There is evidence that people from the general population

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Registry Focus

Patient Perspective

Dealing with my diagnosis of Muir-Torre Syndrome (MTS), subset of Hereditary Non-Polyposis Colon Cancer (HNPCC) and the importance of knowing my family medical history

By R. FitzPatrick

How many of us think of palliative care and saving a life in the same sentence? In June of 2001 a palliative care doctor named Dr. Chin Chung of the Yee Hong Centre did just that. Dr. Chin Chung was my father's doctor and although he could not save his life, he ended up saving mine. While Dr. Chin Chung was caring for my father, he obtained not only my father's medical history, but that of our family's. I remember very well as Dr. Chung was getting ready to leave that day, he turned to me and said "based on what your father has told me, I think you should have your family seek genetic counselling, there may be a genetic reason why your father and other members of your family have gotten cancer." At that time my only concern was for my father, but I knew that this was a very clear message and that it was one not to be taken lightly.

"…there may be a genetic reason why your father and other members of your family have gotten cancer."

It was a very sad day when we learned that my father was diagnosed with melanoma cancer and that it had spread to his liver and spleen. It wasn't the first time that cancer had reared it's ugly head at my father. Eighteen years before he had cancer of the ureter, this resulted in the removal of his left ureter and kidney, followed by radical radiation therapy. These treatments afforded to give my father and our family many more wonderful years together. But this time around we were told he would not be so lucky. Two months later in August of 2001 my father passed away surrounded by our large family in song and prayer. He was a devoted husband, father and grandfather.

Since that time, more than 3 years ago now, I have learnt that some of my family members, including myself, have Muir-Torre Syndrome (MTS), which is a subset of the Hereditary Non-Polyposis Colon Cancer Syndrome (HNPCC). I am thankful to the team at Mt Sinai Hospital working with the Familial Gastrointestinal Cancer Registry to have given me this forum to share a bit about what I have learnt on HNPCC/MTS. To relay how important our family medical history is in enabling us to be more proactive with our own health and the health of our families and future generations of our families. The following is a snippet of my family's experience since that fateful day in June 2001.

After my father's death I was referred to the Toronto Sunnybrook Regional Cancer Centre to the Preventative Oncology Department. I consider myself very lucky to have a team of very capable and compassionate genetic counsellors and doctors there, who are always available to me and my family. We discussed the fact that many of my ancestors on my father's side of the family had been diagnosed with colon cancer in their 40's and 50's and had died of the disease. My father also had many colorectal polyps removed over his lifetime and one of his brother's had been diagnosed with colon cancer in his early 50's. Shortly after my father's death one of his sister's was diagnosed with breast cancer and both my father and my aunt also had many skin lesions including sebaceous adenomas. With all this information the genetic team determined that members of my family were at a high risk of having HNPCC/MTS. We had met the criteria that could put us in the 2-4% of colon cancer patients that have a hereditary form of the disease.

My siblings and I were all recommended to have colonoscopies as soon as possible. It was a scary idea to have such an invasive test, there were awful images in our heads of what we would be put through, but the reality was that the test was really not bad at all. Most of us wouldn't remember a thing after and we all agreed that the worst part of

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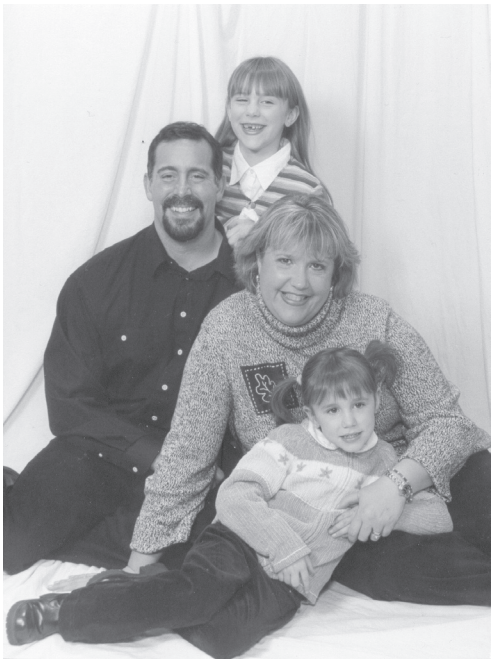
the whole procedure was just drinking the preparation for the test.

Two of my sisters had clear colonoscopies on their first visit as well as my brother. My youngest sister as it turned out was having her colonoscopy the same day as mine at another hospital. It was February 2002 by this time, she had hers in the morning and I had mine in the afternoon. It was a telephone call of mixed emotion when we talked later that day. She had the good news that her colonoscopy was clear but I had to pass on the news that mine was not. During the colonoscopy my gastroenterologist found 2 polyps in my right colon and a small tumour at the rectal sigmoid junction that was too large to remove, but he did do a biopsy. I don't recall him saying the word cancer to my husband and me after the examination. All I do remember is him saying, "You should have your whole colon removed, because of your family history." I had done enough research by that time to know that if something was found, this would be the best course of action.

I had my surgery and as recommended they did remove the majority of my colon. The first step then in confirming that we carried this HNPCC/MTS syndrome was to examine my tumour. It was found to have the features that are commonly seen in the tumours of patients with HNPCC, including a deficiency of the MSH2 gene. My blood then had to be tested, one of the genetic doctors said looking for the mutation 'was like trying to find a spelling mistake in the novel War and Peace, written in Russian, when you don't speak Russian.' This is why it was made clear to me that the testing was a long and trying process. Eventually the mutation was found, confirming my clinical diagnosis.

The impact of our learning we might carry HNPCC/MTS was devastating to my family at first.



Now as the dust has settled, we as a family, … are optimistic for our future.

It was one thing for each of us to know that we may have to deal with a possible life threatening syndrome that causes various cancers, combined with the possibility of major preventative surgery for those who would be determined to have the mutated gene. Just having the genetic testing would be a big decision. The implications of having a positive test result could despite the potential medical benefits have psychological and social risks, including loss of privacy and genetic discrimination. There were concerns about passing the gene on to our children, the availability, or lack of preventive options, and discrimination in employment and the affect on our insurance rates or, worse, our children's ability to obtain insurance coverage in the future.

Now as the dust has settled, we as a family, look at it very differently. We are optimistic for our future. We are now more proactive with our health and likely taking much better care of ourselves than the general public. Thankfully we are surrounded with dedicated, caring and knowledgeable doctors. We feel blessed to have the knowledge we have attained these last few years. I believe that the scale will eventually tip and those who do not do genetic testing will be the ones who have discrimination in insurance matters and all the other concerns that we are currently dealing with. It may not happen in my life time but this is my hope for my children and my future descendants.

Patients with HNPCC have increased risks of getting various cancers. The greatest organs at risk over a life time are the colorectum and endometrium (womb). Because of this I later had a prophylactic complete hysterectomy. Other organs in the gastrointestinal, gynaecological and urinary tract areas are also at increased risk. In my family, we also suspect that breast cancer may be associated with this syndrome. What they also determined was that because my father and aunt had various skin lesions including sebaceous adenomas

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Pediatric Update

By Dr. Carol Durno

"Kids' Korner"

We are pleased to announce the development of a new section on the Mount Sinai Familial GI Cancer Registry website (www.mtsinai.on.ca) called "Kid's Korner". "Kid's Korner" is designed just for kids. The purpose is to provide an opportunity for kids and teenagers to learn more about polyp conditions in a friendly and interesting "kid way". There's lots of graphics and activities, such as making your own family tree for kids to participate in. We welcome your feedback!

Buddy System

Your child may feel like he/she is the only person in the school or town with a particular polyp condition. It can be helpful for kids and teenagers to meet other kids who are going through the same experience. Through the Registry, we offer a buddy system that allows your child and/or family to be in contact with other kids who understand. This is all done on an individual basis. Kids can decide if they want to talk on the telephone to a peer, others may choose email, write letters, or meet in person. We can help match you up with someone who has things in common with you such as being an avid hockey player. Please contact Terri Berk (416) 586-8334 or tberk@mtsinai.on.ca for more information and/or to hook up with a buddy.

Studies you Participated In: Colon Cancer in Adolescents and Young Adults

We have submitted a manuscript reviewing colon cancer in patients diagnosed at 24 years of age and younger. This paper focuses on sixteen patients looking at clinical and genetic factors in this population.

Some of the adolescents and young adults had family histories of early or frequent cancers. In this study colon cancer was seen in a parent of the affected child in almost half of the families. The age of diagnosis of colon cancer in the parent was between 20 and 63 years.

Five children with colon cancer who had cancer-causing gene mutations identified have parents who also carry a mutation that causes colon cancer. This study identified these parents who are at risk of cancer and therefore the parents can participate in regular screening including colonoscopy to monitor for early signs of cancer. All of these parents remain unaffected to date.

Almost half of the children, adolescents, and young adults in this study developed a second cancer during follow-up. The follow-up period ranged from 8 months to thirty years after the initial diagnosis of colon cancer. It's important for these patients to be monitored closely to identify second cancers. ■

Research Update

The MYH Gene and Colorectal Cancer Risk

Dr. Steven Gallinger and Marina Croitoru, Master's Program, University of Toronto

While the majority of colorectal cancers are not well understood from a genetic perspective, a small fraction are clearly caused by inherited genetic mutations that can be passed down from one generation to another. The two well-known inherited syndromes, Familial Adenomatous Polyposis (FAP) and Hereditary Nonpolyposis Colorectal Cancer (HNPCC), account for approximately 2-3% of all colorectal cancer cases. Recently, a new familial syndrome has been identified and found to give rise to multiple intestinal polyps and colorectal cancer. Researchers have concluded that mutations in a gene called MYH are responsible for this inherited form of colorectal cancer termed MYH Associated Polyposis (MAP).

At the Samuel Lunenfeld Research Institute we have conducted a large population-based study of more than

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we also had the subset of HNPCC called MTS.

In 1999 world literature contained only 205 cases of Muir-Torre Syndrome (MTS), so I was not surprised to learn, when I went to various doctors these last few years that they had never heard of it. For families with HNPCC it is important to be aware of this syndrome. The skin lesions that are associated with Muir-Torre Syndrome (MTS) are sebaceous adenomas, sebaceous epithelioma, sebaceous carcinomas, and keratoacanthomas, all of which my father had over his life-time. Interestingly they often appear before or concurrently with an internal organ cancer as they did with both my father and aunt. This I look at now as a red flag, if we had known this before when my father and aunt exhibited with these lesions we would have known to check more closely at the related internal organs which can exhibit cancer under HNPCC/MTS.

Through all of this it has become very clear to me that my father's illness, his subsequent death and the message from Dr. Chung was all part of a greater plan. My cancer was going to make a difference in not only my life but in the lives of many others in my family. I will continue to do research in to these syndromes and get in touch with every family member I can track down to tell them about this syndrome. I hope that the information I have shared about Muir-Torre Syndrome (MTS), will also be explored more with families that have Hereditary Non-Polyposis Colon Cancer (HNPCC).

As it has been done recently in the United States, I am hopeful that our government will also launch a national public health campaign to help focus attention on the importance of family health history. One that would enable individuals at home to enter information about their own family histories and then obtain a printed pedigree they can bring to their physician at the time of their visit and save all of that time, which normally is prohibitive for the doctor to collect and get into the patient's medical record. Tracing the illnesses, not only cancer, suffered by our parents, grandparents, and other blood relatives can help our doctors predict the disorders to which we may be at risk and take action to keep us and our families healthy.

We all can save a life, if we take this first step. I encourage everyone to sit down with their families and talk about their medical history, call a family meeting, talk to the older generations in your family, share what knowledge they have about your ancestors and blood relatives. Share what you have learnt with your family physicians and your other caregivers. Make a difference for your children and your future descendants. ■

Endometrial cancer in families with HNPCC: New Study

By Dr. Katharina Kieser

Endometrial cancer is the 4th most common female cancer in the general population but the second most common cancer in women with HNPCC. Endometrial cancer starts in the lining of the uterus. In most women the cancer is detected at an early stage because there is irregular vaginal bleeding. The endometrial cancer is treated by a hysterectomy and removal of both ovaries. In the general population endometrial cancer is diagnosed at an early stage 75-80% of the time and early stage endometrial cancer is cured more than 85% of the time.

Women in HNPCC families have a 45% lifetime risk of getting endometrial cancer. This is much higher than the 1.5% risk in the general population. To be able to start recommending screening programs or prophylactic surgeries we need to know whether women who get endometrial cancer in HNPCC families get the same type of cancer as those women who are not in these families.

We know that women who get HNPCC related endometrial cancer are, on average, 15 years younger than women who get endometrial cancer sporadically usually in the 40's and 50's.

Currently, women of HNPCC families are encouraged to see a genetic counselor. During this visit a more precise estimate of the risk of endometrial cancer can be given to each patient. Also the signs and symptoms of endometrial cancer to watch for can be discussed. The earliest sign of endometrial cancer is usually abnormal bleeding. For premenopausal women this means bleeding outside of the time of your normal monthly period, which should come about every 28 days, and for postmenopausal women any bleeding. Either of these situations should be discussed with your doctor.

Initial treatment for this cancer is removal of the uterus, cervix, tubes and ovaries. When surgery is complete the samples are sent to the pathologist who looks at them closely under the microscope. The two most important pieces of information from this are; 1) How far has the tumor spread (stage) and 2) What type (histology) is it. This helps the surgeon decide whether more treatment is needed.

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Research Update

1200 people diagnosed with colorectal cancer and over 1200 healthy individuals (controls) to determine the risk of developing colorectal cancer associated with inheriting mutations in one or both copies of the MYH gene. In this study recently published in the Journal of the National Cancer Institute we concluded that carrying a mutation in the MYH gene slightly increases an individual's risk of developing colorectal cancer. Our results confirm previous findings that individuals who carry two mutations in the MYH gene (biallelic mutations) have a high risk of developing colorectal cancer and colorectal polyposis.

Our study is among the first to show an increased risk of colorectal cancer in individuals who carry only one mutation in the MYH gene (monoallelic mutations), although larger studies are necessary in order to verify this association. We found that carriers of mutations in the MYH gene were more likely than non-carriers to have a first- or second-degree relative affected by colorectal cancer, providing further evidence for an increased risk of colorectal cancer associated with carrying one mutated copy of the gene.

We are currently extending our findings to examine the frequency of MYH mutations in patients diagnosed with multiple colorectal adenomas and without mutations in the APC gene which causes FAP. We have identified biallelic MYH mutations in 22% of patients from the Familial Gastrointestinal Cancer Registry at Mount Sinai Hospital. We are now examining whether other family members carry the same mutations and whether they are also affected by colorectal adenomas or cancer. This will help us gain a better understanding of the risk and pattern of disease associated with MYH mutations. ■

Network

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New Study: Endometrial Cancer

We do not know however whether the cancer in women of HNPCC families is just as early when it is detected and whether it has the same histology. Therefore we currently have a study ongoing which compares the stage and histology of endometrial tumors in women with a family history and those without a family history. Some of you will be receiving questionnaires about your endometrial cancer as a part of this study.

This study will be the framework from which we can then consider whether women at high risk for endometrial cancer should be undergoing any screening program in addition to the current detailed genetic counseling and discussion about the signs and symptoms of endometrial cancer.

Thank you for your participating in this study and ongoing studies. By increasing the knowledge about endometrial cancer in women with HNPCC we will help to improve the care the medical community can provide. ■

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Chemoprevention Research Study Update

who take aspirin are less likely to develop colon cancer than those who do not take aspirin. It is not yet known whether taking aspirin protects people with hereditary predisposition to colorectal cancer. One of the goals of this study is to answer this question.

There is also some evidence that high starch content in the diet can reduce the risk for polyps and bowel cancer in the general population. Therefore, the other goal of the study is to look at the effects of a specific type of starch, called resistant starch on polyp growth and tumor development. It seems as though resistant starch reaches the bowel without being digested first, and is actually broken down in the bowel. This process is thought to reduce the chance of a colon tumor forming.

Participation in CAPP2 involves a two-year period of taking a daily regimen of either:

1. aspirin
2. starch
3. both aspirin and starch, or
4. neither (placebo).

Choosing which group you will be in is made randomly by a computer. The subject cannot choose their group which avoids bias in this important study. The study has been approved by our human ethics committee. If you or one of your relatives is interested in learning more about your eligibility or details about CAPP2, please contact Beverly Schmocker, the study coordinator at (416) 586-8286. ■