Lynch Syndrome: Still Not a Familiar Picture

Colorectal carcinoma (CRC) is the second most common cause of cancer deaths in the United States. It affects men and women equally. About 140,000 new cases of colon cancer are diagnosed and about 55,000 patients die from it each year in the US. Colon cancer is so common that a person can have two or more relatives affected with colon cancer due to chance alone, however, in some families it is hereditary. Currently, about 5% of all CRC cases can currently be explained by known inherited tumor syndromes and many of those deaths can be presented through appropriate cancer screening and early detection.

The most common of the known CRC predisposing conditions is Lynch syndrome, which is an inherited disease that increases your risk of colon cancer and other cancers. Lynch syndrome is also known as hereditary nonpolyposis colorectal cancer (HNPCC). In families with the Lynch syndrome, multiple members are affected with colon cancer often at a young age, with the average onset being 45. Cancers of the endometrium (the lining of the uterus), ovary, urinary tract, upper GI system, and biliary tract also occur more often in these families. Lynch syndrome is caused by a mutation in one of the mismatch repair (MMR) genes: MLH1, MSH2, MSH6 or PMS2. A person who has a mutation in a gene associated with Lynch Syndrome would have a much higher chance of developing colon cancer, as well as other cancers, than a person who does not have a gene mutation.

Certain guidelines have allowed the recognition of many affected families, and genetic testing has led to identification of many (asymptomatic) family members at risk for Lynch syndrome. However, an article published in the February 2008 issue of The World Journal of Surgical Oncology reports a lack of awareness about this hereditary tumor syndrome among doctors as well as patients (Hes, 2008). The following case study included a large Lynch syndrome family with 15 affected family members with cancer in 7 organs.

In November 2006, a 56-year old woman diagnosed with endometrial and colon cancer at age 53- and 54-years old visited a clinic for genetic counseling because she was worried about the many cases of cancer in her family. The direct reason for her visit was the recent death of her 39-year old son with rectal cancer. She reported her overwhelming family history, which easily fulfilled the criteria of families that are at risk for Lynch syndrome. Testing on archival tumor material of her colon cancer demonstrated presence of the MSH2 and MSH6 proteins, which is associated with Lynch syndrome. Genetic testing was done and an entire MSH2 gene mutation was found, which confirmed the diagnosis of Lynch syndrome.
In retrospect, some doctors had noticed significant features in this family, but did not take action. First, in 1979, a doctor who was treating a family member consulted a colleague about the very early onset of endometrial cancer, but the colleague reassured him at that time that the age of onset, 41 years old, was not very rare. Second, in 2005, a doctor mentioned possible HNPCC in a family member, who was diagnosed with biliary cancer after she had developed three separate colon cancers, but nothing was done. Third, in 2006, a doctor treating another family member suggested MSI testing on tumor material after his mother had expressed her concern about the family history, but did not proceed.

This family is a fine example of the excess of tumors that may occur in Lynch syndrome. The organ involvement in this family included seven organ systems: colon, uterus, skin, stomach, urinary tract, pancreas and biliary system. This case report shows a considerable delay in diagnosing Lynch syndrome which negatively influenced the management of many family members. None of the family members underwent preventive screening on the basis of the family history, even though surveillance has been shown to decrease mortality in Lynch syndrome families. Consequently, early identification of mutation carriers might have reduced the high and early morbidity and mortality observed in this family.

This illustrates a lack of awareness and knowledge about this hereditary tumor syndrome among doctors as well as patients. Hereditary features, like young age at diagnosis, multiple tumors in multiple organs and a positive family history, should lead to timely referral for genetic testing. For Lynch syndrome, these features can be found in the Amsterdam and Bethesda criteria listed.

Amsterdam criteria II

<table>
<thead>
<tr>
<th>There should be at least three relatives with colorectal cancer (CRC) or with a Lynch syndrome associated cancer: cancer of the endometrium, small bowel, ureter or renal pelvis.</th>
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<tbody>
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<td>o one relative should be a first-degree relative of the other two</td>
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<td>o at least two successive generations should be affected</td>
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<td>o at least one tumor should be diagnosed before the age of 50 years</td>
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<td>o FAP should be excluded in the CRC case if any</td>
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<td>o tumors should be verified by histopathological examination</td>
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Bethesda guidelines

| CRC diagnosed in a patient aged <50 years. |
| Presence of synchronous, metachronous colorectal, or other Lynch syndrome-related tumors, regardless of age. |
| CRC with MSI-high phenotype diagnosed in a patient aged < 60 years. |
| Patient with CRC and a first-degree relative with a Lynch syndrome-related tumor, with one of the cancers diagnosed aged <50 years. |
| Patient with CRC with two or more first-degree or second-degree relatives with a Lynch syndrome-related tumor, regardless of age. |

Update On EDRN Grant Projects

Two new EDRN projects were introduced to eligible Registry members in 2006. New Registry members are being invited to participate in these studies upon completion of enrollment.

One project is called the Longitudinal Serum Biorepository. All High Risk Registry members are invited to participate in this biorepository. Participation involves having a serum and plasma blood sample drawn each year and shipped to Creighton University for processing and storage. If pre-cancerous or cancerous lesions should develop in a participant, any previously drawn serum/plasma samples will be invaluable to researchers in their search for early cancer detection signals in the blood.

Another project involves carriers of gene mutations that put them at risk for Hereditary Nonpolyposis Colon Cancers (HNPCC). The purpose of this study is to determine if colon adenomas or cancers can be detected by tests of stool or serum. Blood and stool samples will be collected from consenting individuals who are scheduled for a colonoscopic exam.

Eligible Registry members should have received information regarding these studies. If you have not received study enrollment materials for one or both of the above projects and believe that you should have, please contact Annie Williams, High Risk Registry Coordinator at (402) 280-3189, (800) 648-8133, extension 3189 or andreawilliams@creighton.edu.
Registry Recruitment Update

The High Risk Registry began mailing Early Detection Research Network (EDRN) and Registry information to potential participants in March of 2001. Short update questionnaires are forwarded to all Registry members at one year intervals from their Registry enrollment date. These questionnaires help us identify if a participant has a new diagnosis of cancer from the previous year and this aids us in our research.

The National Cancer Institute’s Early Detection Research Network is developing a number of genomic- and proteomic-based biomarkers, some are being validated. More information about this program can be found on the Internet at: http://edrn.nci.nih.gov/.

The following centers are currently distributing Registry recruitment materials:
Aegis Women's Healthcare (Bloomington, IN)
Alexian Brothers Hospital Network (Chicago, IL)
Allegheny General Hospital (Pittsburgh, PA)
Breastlink Medical Group (Long beach, CA)
Children’s Medical Center (Dayton, OH)
FAP Support Group (Atlantic City, NJ)
Geisinger Medical Center (Danville, PA)
GeneWISE (Slingerlands, NY)
Harvey Institute for Human Genetics (Greater Baltimore Medical Center)
Holy Cross Hospital (Fort Lauderdale, FL)
Indiana University Northwest (Gary, IN)
Inland Northwest Genetics Clinic (Spokane, WA)
Main Line Health System – Lankenau Hospital (Wynnewood, PA)
Markey Cancer Center (Lexington, KY)
Michigan State University (East Lansing, MI)
Minnesota Colorectal Cancer Initiative (St. Paul, MN)
Northeast Health Genetic Services (Green Island, NY)
St. Vincent’s Family Life Center (Indianapolis, IN)
St. Vincent’s Hospital (Green Bay, WI)
Tulane Human Genetics Program (New Orleans, LA)
Unity Hospital (Fridley, MN)
University of Arkansas for Medical Sciences (Little Rock, AR)
University of Florida Shands Cancer Center (Gainesville, FL)
University of Rochester Medical Center (Rochester, NY)
Vanderbilt University Medical Center (Nashville, TN)
Vermont Regional Genetics Center (Burlington, VT)
Waukesha Memorial Hospital (Waukesha, WI)
Wellmont Holston Valley Medical Center (Kingsport, TN)
Wright State University (Dayton, OH)

Your participation in the High Risk Registry is greatly appreciated. This unprecedented endeavor in cancer research provides a promising opportunity to improve medical practice in relation to cancer prevention. If you have any questions or concerns, please contact Annie Williams, High Risk Registry Coordinator at (402) 280-3189, (800) 648-8133 extension 3189 or andreawilliams@creighton.edu.
Early Detection Research Network Staff

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We would like to introduce our new EDRN Registrar, Andrea Williams RN,MSN. Andrea comes to us experienced in Genetics and is here to answer questions and help you in any way possible.

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Henry Lynch, MD, Principal Investigator htlynch@creighton.edu
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Was this newsletter forwarded to you? Do you have a move coming up in the near future? Please keep the EDRN High Risk Registry informed of your current mailing address. You may call or e-mail us with your address update or complete and mail the address update form. Also if there have been recent changes in your medical history, please call the Registry at one of the numbers listed below.

(402) 280-3189 OR (800) 648-8133, extension 3189 andrewilliams@creighton.edu

Name ______________________________________________________________________________
Address_____________________________________________________________________________
City, State, Zip_______________________________________________________________________
Telephone (Day) _____________________________________________________________________
Telephone (Evening) __________________________________________________________________

Mail completed forms to: Creighton University Medical Center
EDRN High Risk Registry
Department of Preventive Medicine
2500 California Plaza
Hixson-Lied Science Building, Room 202
Omaha, NE 68178

We’re on the Web http://medicine2.creighton.edu/EDRN-Registry