University of Wisconsin
Paul P. Carbone Comprehensive Cancer Center
Advances
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With Rat Genome As Guide,

Human Breast Cancer Risk Defined

Terry Devitt, University Communications

Combing the genomes of the rat and the human, researchers at the University of Wisconsin-Madison have found swaths of genetic code that can be used to assess the risk of human breast cancer.

The new work by a team of researchers at UW-Madison's McArdle Laboratory for Cancer Research represents some of the early potential clinical payoffs of the massive efforts to gather and sequence the genomes of humans and other animals.

> "At the end of the day, not only have we found these markers in humans, but we have the animal model to test prevention and treatment strategies."
>
> —Michael Gould, PhD
> McArdle Laboratory
> for Cancer Research

Writing in the April 2 issue of the Proceedings of the National Academy of Sciences (PNAS), a team led by Wisconsin oncologist Michael N. Gould reports the discovery of genetic variations on regions of the human genome "that significantly associate with breast cancer risk in women."

One of the newly identified regions of the human genome, known as a "resistance locus," means that, on average, women who have it have a 15 percent decreased risk of breast cancer. Another region, which acts in a recessive manner, increases risk of disease by as much as 19 percent for the average woman.

The discovery is important because it could underpin new genetic screening methodologies for the most common type of cancer in American women. Instead of focusing on individual genes that may protect or predispose an individual to cancer, the new work demonstrates that identifiable patches of genetic code that do not always contain protein-making genes play a role in the onset of disease.

Unlike current genetic strategies for assessing breast cancer risk, which involve looking for mutations of two specific genes known as BRCA1 and BRCA2, the Wisconsin study identifies risk associated with areas of the genome that harbor so-called modifier genes, genes that do not make proteins, as many genes do, but instead act to influence other genes elsewhere on the genome and that help initiate the cascade of events that leads to breast cancer.

"Scientifically, this is unique, and we can use this new knowledge to study risk in the average woman," says Gould, a member of the UW Paul P. Carbone Comprehensive Cancer Center (UWCCC). He adds that while mutations of the BRCA genes are good predictors of cancer risk in an individual, they are uncommon, occurring in less than 1 percent of women and are thus too rare to be used effectively for breast cancer screening. As many as 200,000 new cases of breast cancer are reported each year in the United States and upward of 50,000 people die annually as a result of the disease.

"This could be used to screen the general population," says Gould of the work that utilized a rat model for breast cancer to find regions of the genome that seemed to influence the onset or prevent the disease. Knowing the regions of the rat genome important for breast cancer, Gould and his colleagues were able to identify similar regions on the human genome using data obtained from samples provided by nearly 12,000 women from Wisconsin and the United Kingdom.

The genetic variations found by Gould and his team occur on a portion of the genome that has no obvious direct function, such as making proteins. The implication is that the swath of genetic code identified by the Wisconsin group contains modifier components of the genome, which act at a distance to influence what other genes do.

Michael N. Gould, oncologist with the McArdle Laboratory for Cancer Research at the University of Wisconsin-Madison, poses in his lab. Gould led a team of researchers that identified variations on regions of the human genome "that significantly associate with breast cancer risk in women." The team used Gould's rat model for breast cancer to help identify the suspect areas of the human genetic code.

Scientists believe that breast cancer and many other diseases result from a complex series of genetic events. They suspect that modifier loci play a big role in many types of diseases, but finding such genes has proved exceptionally difficult, Gould says. Thus, the new work adds an important new piece to the molecular puzzle of breast cancer and, according to Gould, is a strategy that is also now being employed to unravel the secrets of other diseases such as diabetes.

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The rat model for breast cancer, developed by Gould's lab during the past decade, provides a unique window to the molecular levers that influence disease. The rat is a good model for breast cancer because the disease manifests itself in the animal in much the same way it occurs in humans.

Using the model, Gould's team was able to home in on eight areas of the rat genome that dispose or protect the animal from breast cancer. Then, scouring the human genome, it was possible to identify similar regions of genetic code that have been preserved throughout the course of evolutionary history.

"We scanned the whole genome of the animal (rat) model for breast cancer," Gould explains. "We mapped several regions in the rat genome that were associated with susceptibility to mammary cancer."

Using data from cancer patients, Gould's team was then able to identify parts of the human genome that had similar variations that either increase or decrease the risk of disease.

An ability to screen women and assess breast cancer risk promises to help with prevention and early detection of the disease. Gould also believes that the knowledge may help spur new strategies for prevention and treatment.

"At the end of the day, not only have we found these markers in humans, but we have the animal model to test prevention and treatment strategies," he says.

The work in Gould's lab was spearheaded by David J. Samuelson, Stephanie E. Hesselson and Amy Trentham-Dietz. Bruce A. Ponder of the University of Cambridge is also a senior author of the new PNAS report. The work was funded primarily by the National Institutes of Health.

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Understanding the value of dietary supplements

Paul Hutson, PharmD

Q: Should I take botanicals or vitamins during chemotherapy, radiation therapy, or after treatment to protect my healthy cells from the toxicity of treatment and to prevent recurrence?

A: Cancer patients, their friends and family, seeking ways to boost the effectiveness of treatment and minimize side effects, often look to dietary supplements. The media and marketers also generate interest in natural products or vitamins. Having so many choices makes it difficult to determine what supplements can or should be part of cancer care.

Patients need to focus first on a balanced diet which emphasizes fruits, vegetables, fish and whole grains. Dieticians can help them develop tasty, nutritious and quick-to-prepare meal plans to use during and after treatment. Drinking green tea is also an option; recent laboratory studies demonstrated tea extracts may suppress the growth of several types of cancer. Daily multivitamins are also appropriate.

Some women consider using soy protein and extracts such as genistein while being treated for breast cancer. Marketers and some scientists suggest soy flavonoids act like tamoxifen or raloxifene, and also may inhibit cellular growth. Unfortunately, the concentrations of genistein and other flavoinoids needed to inhibit cellular growth are far greater than those available in even large doses of soy protein or genistein extracts. More importantly, the long term effect of soy on hormonally-stimulated cancers such as breast cancer is unknown, and there is no evidence that increased soy or soy extracts decrease the risk of cancer recurrence.

Many breast cancer patients who are taking tamoxifen, and some prostate cancer patients using hormone blockers, experience menopause-like symptoms and may consider dietary supplements such as soy, soy extracts, red clover, black cohosh, vitex, evening primrose oil, and dong quai. Most studies show that when compared against a placebo, there is little benefit of botanicals for menopausal symptoms. There is also an unknown likelihood that the extracts may stimulate the growth of any microscopic, residual disease.

St. John's wort, commonly used to treat depression, should not be used by chemotherapy patients. It has been proven to increase the rate of removal of many drugs, which decreases the concentration of many chemotherapy drugs, hindering their effectiveness.

Chemotherapy and radiation patients sometimes wonder about using antioxidants or vitamin replacements to protect normal cells from toxic treatments. There is no clinical evidence showing large amounts of antioxidants decrease the overall toxicity of chemotherapy, and taking high doses of antioxidants may actually lower the ability of state-of-the-art radiation therapy, such as tomotherapy, to kill cancer cells.

When contemplating dietary changes, patients should also consider how cancer treatment affects their long term health, particularly the impact on their cardiovascular and bone structure. Aging decreases bone density, but hormone blockers for prostate or breast cancer accelerate this bone weakening. Patients must ensure they are taking sufficient calcium, about 1 to $1\,^{1/2}$ grams daily, especially in Wisconsin where many people are Vitamin D deficient. In addition, there is early evidence that Vitamin D-like drugs may have anti-tumor effects, especially for prostate cancer.

For cardiovascular health, research has shown that fish and fish oil may decrease blood triglyceride concentrations, and that dietary fiber and soy decrease cholesterol. A daily glass of red wine, purple grape juice or cranberry juice also has demonstrated benefits.

Most clinicians encourage patients to concentrate on a well-balanced meal plan that provides energy and the needed combination of nutrients rather than relying on botanical supplements and megavitamins.

Paul Hutson, PharmD, is a pharmacist and associate professor in the University of Wisconsin School of Pharmacy. In addition, he is an associate member of the UW Paul P. Carbone Comprehensive Cancer Center, and has a clinical research focus on symptom management and palliative care.

MARK YOUR CALENDARS

Jack Stoltz Memorial Golf Outing
Old Hickory Country Club - Beaver Dam, WI
July 23, 2007
(608) 219-0080 or mbradley@metastar.com

Heads Up! Golf Outing
University Ridge Golf Course - Madison, WI
July 30, 2007
(608) 263-1677 or
ajohnson@uwccc.wisc.edu

Sammy Cup Golf Outing
Sycamore, IL
August 4, 2007
amicmo@comcast.net

Walk with G.R.A.C.E.
Richland Center, WI
August 10-11, 2007
www.walkwithgrace.com

Drive for Hope Golf Outing
Maple Bluff Country Club - Madison, WI
August 13, 2007
1-800-252-2664 or driveforhope@cues.org

HEADRUSH
Blue Mounds State Park - Blue Mounds, WI
September 15, 2007
(608) 469-8304 or
headrush@headrushevent.org

Free Multiple Myeloma Education Day
Country Springs Hotel, Pewaukee, WI
September 29, 2007
sandra.lardinois@lls.org or call
(800) 261-7399

Tune It Up!
Orpheum Theatre - Madison, WI
September 14, 2007
(608) 263-1677 or
ajohnson@uwccc.wisc.edu

A Jewel of an Evening
Monona Terrace - Madison, WI
September 19, 2007
(608) 263-1677 or ajohnson@uwccc.wisc.edu

Tim Eagle Memorial Golf Outing
Milan, IL
October 6, 2007
kathy.eagle@fritolay.com

Breast Cancer Research Ride
Janesville, WI
October 6-7, 2007
Sandy Bingham at (608) 752-7256

Click to Cure Cancer Online Auction
www.clicktocurecancer.com
October 12-22, 2007

6th Annual Fall Conference for Health Professionals
Living with a Cancer Diagnosis:
Issues of Long-Term Survivorship
October 19, 2007
(608) 263-0160 or meyers@uwccc.wisc.edu

Visit cancer.wisc.edu for more details on all events listed.

Click to Cure Cancer coming soon

The UW Paul P. Carbone Comprehensive Cancer Center, in conjunction with Clear Channel Radio-Madison and Charter Communications, is pleased to announce the 2007 Click to Cure Cancer auction. Click to Cure Cancer is an online auction, scheduled to run October 12-22, 2007. Proceeds from the event will benefit groundbreaking cancer research and patient services at the UW Carbone Cancer Center.

This easy-to-use auction will include unique items from throughout the area. Similar to a silent auction, participants go to **www.clicktocurecancer.com**, review the items available for bidding and place their bids. Winners will be notified via e-mail at the close of the online auction.

Do you have a unique item to donate for the auction? Please contact Craig Robida at the Cancer Center, (608) 263-4982. And make sure to check out the online auction, October 12-22, 2007!

Helping Patients Maintain the

Best Quality of Life Possible

When the new palliative care unit opens this fall at UW Hospital and Clinics, it will mean much more than adding 10 new beds. It will help break down barriers in health care and become a transition point in patient care, according to James Cleary, MD, a UW Paul P. Carbone Comprehensive Cancer Center specialist in palliative care.

"The new unit will help integrate the passage from treatment through other stages of care," says Cleary. "It will prevent and relieve suffering, and improve the quality of life for patients with serious illnesses."

Palliative care staff typically work along side the primary care team to help patients develop a comprehensive plan for care as a disease advances, assisting with decision making for treatment options, managing symptoms and providing emotional support.

The unit will be available to patients from all areas of the hospital, including the Emergency Room. Whether coming from oncology, general medicine, ICU, or other units, Dr. Cleary and his staff will care for any patient with a life-limiting illness.

"A great example would be stroke patients," says Cleary, "if there is no surgical or other intervention available, we'll be able to keep them comfortable in the palliative care unit."

Cleary is one member of an interdisciplinary team that administers palliative care at UW Hospital and Clinics. Along with nurses, social workers, chaplains and other professionals, he works with any patient seeking comfort, although most are usually approaching death.

"I once had a patient who was in pain because of a spiritual crisis," explains Cleary. "He had committed some misdeeds earlier in life, and he was scared he was not going to heaven."

Although morphine and other pain medications were available, Cleary chose to help the patient in a different manner.

"I couldn't tell him he was going to heaven, but I could certainly lessen his pain by helping him cope with his anxiety," says Cleary. "Spirituality does not just have to be about a single religious view, I can talk about life with patients too."

"The overall focus of the program is to help patients maintain the best quality of life possible," says Kate Ford Roberts, associate clinical nurse specialist in palliative care.

She stresses that palliative care seeks to be consistent with a patient's goals and choices for care. Often, as patients approach death, their priorities shift from therapy and prolonging life to comfort and quality of life.

"As people become less active, and when cure oriented treatment comes to an end, palliative care becomes a much more attractive option," she explains.

However, palliative care patients can receive treatment regardless of life expectancy, which distinguishes the program from hospice care.

The unit will also be family-centered, featuring a family room and small kitchen. Visiting hours will not be enforced.

"We want to make it as home-like as possible in a hospital," says Roberts. "Palliative care does not just treat patients; it works with their family and friends as well."

Members of the palliative care team offer care and support specifically to family members, and help them with advance care planning. They also follow up with the family after the death of their loved one.

When the unit opens, it will bring to reality a 14-year vision for Cleary. It also reflects the changing culture of health care in the United States.

"It is a model of care that is supported by the World Health Organization," says Cleary.

Cleary and Roberts agree that both hospital patients and those who are homeward bound will be the ultimate beneficiaries of the new unit.

"For those who go home, as well as those who never go home, it's the quality of the days and weeks that are left that concerns the palliative care team," said Roberts. "Our focus is to make each day as good, meaningful and symptom free as possible."

New American Family Children's Hospital will

Enhance Cancer Care for Kids

Two words that ideally should never go together are "childhood" and "cancer."

While childhood cancer is today both rare and—in about 80 percent of instances—curable, a child's cancer diagnosis is one of the most devastating things that can happen not only to the child, but the entire family.

Fortunately for families who need it, Wisconsin is about to open the doors of a brand new, state-of-the-art children's hospital. Four years in the making, the six-story American Family Children's Hospital in Madison will replace the existing UW Children's Hospital currently located within the UW Hospital and Clinics building that opened in 1979.

As more parents want to be with their children around the clock, the need for a more spacious, stand-alone children's hospital continued to grow over the past generation.

"With much larger patient rooms and many family-friendly amenities, the American Family Children's Hospital will make life a little less stressful for childhood cancer patients and their families," says Paul Sondel, MD, who heads the Pediatric Hematology/Oncology Division at the UW.

"Our new Hematology/Oncology inpatient unit includes 16 rooms, four of which are earmarked for patients who undergo very complex bone marrow transplants," Sondel says. "In addition, our cancer patients will have their own hospital school room, teen lounge, play room, exercise and rehabilitation room, and family lounge area. Each of these spaces will be within an environment that provides special protective air flow to minimize the risk of infection to our patients."

Donna Sollenberger, president and CEO of UW Hospital and Clinics, echoes Sondel's enthusiasm for the new hospital.

"We cannot wait to unveil this incredible resource to the community," she says. "Most families, thankfully, will never see their child hospitalized. Should the need arise, however, any child, parent, grandparent or friend that enters our hospital will be awed by this facility that is designed around a child's and family's every need."

Plans for the new hospital, which is funded by a combination of private philanthropy and hospital bonding, were first announced in 2003 when American Family Insurance announced a $10 million gift to spearhead the "No Finer Gift" fundraising campaign.

More information about the American Family Children's Hospital is available by visiting **nofinergift.org** or by calling (608) 262-7665.

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Pink Bike Rack

Advances Cancer Research at UWCCC

It often feels that everyone you know, each family you meet, has been touched by cancer in some way. One very extended Wisconsin "family" has found a unique way to remember their special cancer patient and to advance breast cancer research at the same time.

In the late 1980s, Mary Hendrickson-Johnson, the sister of Madison resident, Sara Fortune, had her own battle with cancer. During her treatments, the Fortune and Hendrickson families developed a close relationship with Dr. Paul P. Carbone, former director of the University of Wisconsin Paul P. Carbone Comprehensive Cancer Center (UWCCC), and international expert on breast cancer treatment and research.

This spring, Sara, her husband Chris, and the staff of their Madison-based bike rack and performance cycling equipment company, Saris Cycling Group, decided to make a difference. In memory of her sister, and in recognition of the many thousands of people facing breast cancer each day, they have chosen to help raise dollars for state-of-the-art treatment and research at UWCCC.

"To show our support to the cancer center," says Sara, "Saris is offering one of our most popular bike racks, the Bones™ rack, in a vivid cause-conscious pink. A portion of the proceeds from each sale will go to the Center."

"We are privileged to have the only designated comprehensive cancer center in Wisconsin," says Sara. "The Carbone Cancer Center plays a meaningful role not only throughout the Midwest but at Saris Cycling Group and in our own personal lives.

Chris explains their vision, "With the support of the people of Madison, Wisconsin and communities worldwide, we will strive to cure our family and friends

Chris and Sara Fortune

who are struggling with cancer, as well as support the continued research that is so vital to finding a cure for this disease."

They add, "We are honored to contribute to this world-class center and support the economy of Madison, Wisconsin by manufacturing all of our bicycle racks locally, including the pink Bones™ rack."

To learn more about the Saris Cycling Group family and the pink Bones™ program, visit *www.saris.com*

STUDY: Pomegranate Juice may help fight lung cancer

Hasan Mukhtar, PhD

Research is adding to the reputation of pomegranates as a cancer fighter. A recent study by UW researcher Hasan Mukhtar, PhD shows that consuming pomegranates could potentially help reduce the growth and spread of lung cancer cells or even prevent lung cancer from developing.

In the April 1, 2007 issue of *Cancer Research*, researchers led by Mukhtar, co-leader of the Cancer Chemoprevention Program of the University of Wisconsin Paul P. Carbone Comprehensive Cancer Center (UWCCC), demonstrate that drinking pomegranate fruit extract helps slow the growth of lung cancer in mice.

"Pomegranate fruit continues to show great promise," says Mukhtar, professor of dermatology at the University of Wisconsin School of Medicine and Public Health.

"We have earlier shown that pomegranates contain very powerful skin and prostate cancer-fighting agents. These recent findings expand the possible health benefits of the fruit to the leading cause of cancer death in the country and worldwide, lung cancer. " In other studies, the fruit has been shown to suppress inflammatory cell signaling proteins in colon and prostate cancer.

The research team examined the effect of drinking pomegranate fruit extract on the growth, progression, blood vessel development and signaling pathways in two mouse lung tumor protocols. The dosage of juice extract, delivered to the animals through drinking water, was comparable to what humans could reasonably consume in a day. Mice who were exposed to cancer-inducing chemicals and who were treated with pomegranate juice had significantly lower lung tumor growth than mice treated with carcinogens only.

Researchers say the key to the cancer-fighting capabilities of the pomegranate lies in its abundance of anti-inflammatory antioxidants, and that delaying the process of lung cancer development could be an important strategy to control this disease. Mukhtar added that the use of fruits and vegetables endowed with cancer-fighting properties is the best way to achieve this goal.

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Making a Difference

Pictured (L to R) are Culver's of Middleton owner Scott Goetz, manager Heidi Pease, and Jeremy Watrud at the Cancer Center's annual "Celebration of Life" cancer survivors picnic in May. Each spring, Culver's of Middleton generously donates an ice cream sundae bar for the more than 200 survivors and family members in attendance at the picnic. The Cancer Center would like to extend a huge thank you to Culver's for making a difference with their tremendous support of this event since its inception. To be added to the mailing list for this annual picnic celebrating the strength and courage of anyone affected by cancer, please contact Ann Johnson, (608) 263-1677 or ajohnson@uwccc.wisc.edu.

Saturday, April 28 saw more than 100 people and 80 bikes participating in the first-ever Hump Run motorcycle ride fundraiser. The 100-mile bike trek included several cancer survivors and even some current cancer patients. The event started and ended in Westport, just outside of Madison. The first annual event raised more than $1,800 for gynecologic cancer research and services at the UW Carbone Cancer Center. Thank you to all involved for your generous donation to the Cancer Center.

YES! I want to make a difference by giving to the University of Wisconsin Paul P. Carbone Comprehensive Cancer Center.

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Please call **(608) 263-1677** with questions.

Updates in *Clinical Trials*

Clinical trials are UWCCC's key to progress in the battle against cancer

Breast Cancer

The UWCCC is participating in a national trial for early-stage breast cancer using standard treatments, but changing the process by which patients and doctors determine the best treatment for their cancer. This study, called TAILORx-Trial Assigning Individualized Options for Treament (Rx), is to learn which patients would benefit from receiving chemotherapy and to reduce the use of chemotheraphy in patients who would not benefit. The study uses a 21-gene test to determine the "recurrence score," the likelihood of breast cancer recurrence within 10 years of initial diagnosis. The recurrence score is determined by submitting the original tumor after the initial surgery for the Oncotype DX Assay, developed by Genomic Health, Inc. When the score is assessed, patients scoring in the "intermediate" range are randomized to hormonal therapy with chemotherapy, or hormonal therapy alone. The "low" range patients receive hormonal therapy alone, and the "high" range patients receive chemotherapy followed by hormonal therapy.

This study is open to women who are estrogen-receptor and/or progesterone-receptor positive and HER2-neu negative, have no lymph node involvement, and who are medically appropriate candidates for chemotherapy.

Gastrointestinal Cancer

The UWCCC gastrointestinal oncology research group is sponsoring a phase I/II study of oxaliplatin, capecitabine and sorafenib for patients with stage IV pancreas or cholangiocarcinoma (cancer of the bile duct) who have had up to one prior line of chemotherapy. The primary investigator for this study is Noelle LoConte, MD. The capecitabine is given in a unique way, over only two days, rather than the usual 14 days, along with oxaliplatin. This is a regimen designed by UW's Daniel Mulkerin, MD and has previously been evaluated in a phase I study as well as a phase II study in colon cancer, both done at the UW. It is hoped that this regimen will have less hand-foot syndrome, which is a common toxicity for both capecitabine and sorafenib when given in the usual format. This trial will also evaluate the use of a survey designed by UWCCC's Kyle Holen, MD to determine side effects from treatment and to determine whether this survey is more accurate than clinical assessments. The current trial is expected to be open in the late summer and will enroll patients through the UWCCC, and participating Wisconsin Oncology Network sites.

Lung Cancer

A clinical trial that studies erlotinib combined with a new agent called RAD001 recently opened at UWCCC. Erlotinib is an FDA- approved treatment for non-small cell lung cancer that works by inhibiting EGFR (epidermal growth factor receptor). EGFR is seen in more than half of non-small cell lung cancer tumors. RAD001 is a new drug that works by stopping the division and growth of cancer cells. Combining these therapies will target two different cellular pathways to try to slow the growth of lung cancer tumors.

Patients will take RAD001 either daily or weekly, in combination with erlotinib once daily. The study is open to patients with non-small cell lung cancer who have been previously treated with chemotherapy.

For more information about these and other clinical trials at the UW Paul P. Carbone Comprehensive Cancer Center, contact Cancer Connect, (800) 622-8922 or (608) 262-5223 in the Madison area.

A complete listing of clinical trials at the UWCCC is also available on our website, www.cancer.wisc.edu