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Gene Variant May Identify Cirrhosis Patients at High Risk of Liver Cancer

Researchers from Massachusetts General Hospital have found that a single nucleotide polymorphism (SNP)—a change in a single unit of DNA—in the *epidermal growth factor* (*EGF*) gene may significantly increase the likelihood that a patient with cirrhosis will develop hepatocellular carcinoma (HCC).

HCC is difficult to treat and most commonly arises in patients with cirrhosis, often caused by chronic infection with the hepatitis B or C viruses. The results of this study, published in the January 2 *Journal of the American Medical Association*, may help identify a subset of patients who would benefit from intensified screening and possibly chemoprevention strategies.

The investigators focused on a SNP in the *EGF 61*G* allele, in which one or both copies of a specific adenine nucleotide (A) in the *EGF* gene are replaced with a guanine nucleotide (G). Previous work in both cell cultures and animal models showed that this SNP plays a role in raising EGF protein levels, and EGF has been implicated in liver tumor formation in animals.

"We deliberately chose to focus on one SNP that had previous data suggesting that it's functional" in carcinogenesis, explained Dr. Kenneth Tanabe, lead author of the paper.

The researchers examined DNA from all 207 patients with cirrhosis who had blood or tissue stored in the Massachusetts General Hospital Cancer Center Tumor Bank between 1999 and 2006. Of these patients, 59 developed HCC.

Patients with one copy of the SNP (*A/G* genotype) were more than two times as likely to develop HCC, and patients with two copies (*G/G*

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Cancer Research Highlights

Sunitinib Linked to Heart Failure and Hypertension

Patients taking sunitinib (Sutent) should be monitored for cardiovascular side effects such as hypertension and signs of heart failure, especially those patients with a history of coronary artery disease or cardiac risk factors, a team of oncologists and cardiologists said last month in *The Lancet*. The recommendation is based on evidence of cardiac side effects among some patients taking sunitinib to treat gastrointestinal stromal tumors (GIST). Sunitinib is approved to treat advanced renal cell carcinoma and metastatic GIST after resistance to imatinib (Gleevec) develops.

Dr. Ming Hui Chen of Harvard Medical School and her colleagues

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Director's Update

Coding Cancer Research Accurately

One of the truly unique aspects of NCI is its close relationship to the cancer community, a relationship made possible by the special authorities granted by the National Cancer Act of 1971. Those authorities include the mandate for robust and frequent communication about the Institute's research priorities and activities, including its support of research grants pertaining to organ sites.

In that light, I wanted to raise awareness about a worrisome new initiative that will change how NIH institutes and centers (ICs) track and report the research they fund. A result of requirements in the NIH Reform Act of 2006, these changes in grant activity reporting are intended to establish stronger, more transparent processes for how all ICs manage their research portfolios through coding of individual awards. It's a laudable objective, but as the old adage says, "The devil is in the details."

In approximately 1 year, NIH plans to roll out the Research, Condition, and Disease Categorization (RCDC) electronic coding system. This system is designed to categorize and catalogue the projects and grants supported by NIH using one central database. The RCDC will include 340 research categories, each with new definitions that will be used to electronically sort ICs' research projects and programs.

In presentations at the most recent meetings of the National Cancer Advisory Board (NCAB) and the NCI Board of Scientific Advisors (BSA), representatives from the NIH Office of Portfolio Analysis and Strategic Initiatives (OPASI) explained how the RCDC will work.

While members of both NCI boards and NCI senior leadership support efforts to create more sophisticated portfolio analysis tools, concerns were raised about whether this new centrally managed coding system could adequately code and track "cancer research." Of particular concern is how basic science will be reported under the RCDC, which as currently formulated, does not adequately capture basic research as a category. Basic discovery is fundamental to understanding the underlying biology of carcinogenesis and tumor progression—and accounts for a substantial cancer research investment that deserves accurate coding and reporting. Complicating basic science reporting further is how to report projects, for example, on signaling pathways that might impact several cancer types. Until questions surrounding coding of basic research are more clearly resolved, there is a real concern that the RCDC could potentially miss, and therefore underreport, NCI's support of basic research.

NCAB and BSA members correctly noted that the complexity of cancer is not easily categorized electronically. NCI has developed a robust system for coding and reporting the research projects it supports, using experienced indexers who ensure that a given project's contributions are adequately captured and reported. This system, which has been refined by NCI over many years, allows dollars attached to each research project to be prorated over specific categories. A real concern by NCI with the proposed RCDC system, which does not prorate projects, is the likelihood of significant misrepresentation of exactly how cancer research dollars are spent. It is difficult to establish an electronic system that can adequately replace expert coders, trained to carefully evaluate each grant, particularly when trying to categorize complex cancer biology research programs.

Board members also voiced their concern that the RCDC cannot account for a large amount of NCI funding that goes to support the extramural cancer research infrastructure, including the NCI-designated Cancer Centers, Cooperative Groups, and NCI's Specialized Programs of Research Excellence (SPOREs).

In short, there is a fear that the RCDC could, in fact, result in a less accurate, less transparent accounting of cancer research support. Finally, the boards felt that the long-standing processes established by NCI for communicating this information to the public, Congress, and the advocacy community would be lost—resulting in confusion and apprehension, especially among the numerous cancer advocacy organizations.

NCI leadership has shared these concerns with OPASI staff and requested that "cancer research" be exempted from the RCDC reporting requirements, as will be done for "AIDS" and "biodefense" research. We are currently working with OPASI leadership to determine if processes can be established so that the coding and categorization that NCI already does can be

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Cancer Research Highlights

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retrospectively analyzed the medical records of 75 GIST patients treated at the Dana-Farber Cancer Institute during a phase I/II study. A total of 11 percent of patients had a cardiovascular event—two patients had heart attacks and six others experienced heart failure. In addition, 47 percent of patients developed hypertension—systolic and diastolic blood pressure increased during the first cycle of treatment—and 20 percent had reduced heart function.

Most cardiac problems including hypertension were manageable and the majority of patients with heart failure resumed sunitinib therapy. Histories of coronary artery disease and/or hypertension were predictors of cardiovascular events.

Cardiac side effects have been reported for other successful targeted cancer drugs such as trastuzumab (Herceptin) and bevacizumab (Avastin). The study supports a growing view that oncologists and cardiologists need to work together to identify the cardiac side effects of new, targeted drugs and to manage cardiac health throughout therapy.

"The paradigm remains to treat the cancer while caring for the heart," said Dr. Chen, a cardiologist who specializes in the cardiac health of adult cancer patients. She noted that although the cardiotoxicity in this study was not seen in phase III trials, the patients may be more similar to patients in the general population now being treated with sunitinib.

A letter in the January 3 *New England Journal of Medicine* reports on 14 patients with metastatic renal cell carcinoma who also experienced rapid, marked increases in blood pressure during treatment with sunitinib. The effect was revealed by home blood-pressure monitoring and had been missed during routine office visits.

"Our study suggests that rapid and large increases in blood pressure should be anticipated in patients who are treated with sunitinib," conclude the authors from Hôpital Européen Georges Pompidou in Paris.

Cancer Doctors May Need Training on Empathy Skills

Cancer specialists (oncologists) may need additional training to encourage patients to express their concerns and negative emotions and to respond empathically to these concerns, researchers recommended in a study published December 20, 2007, in the *Journal of Clinical Oncology*.

The report presented data from the Studying Communication in Oncologist-Patient Encounters (SCOPE) project, an NCI-funded, three-site study from Duke University, the Durham Veterans Affairs Medical Center, and the University of Pittsburgh. It is based on results from 398 clinic conversations between 51 oncologists and 270 patients with advanced cancer. The study found that the oncologists encountered few empathic opportunities during their patient meetings (37 percent of visits) and responded with empathic statements infrequently (only 22 percent of the time).

Empathic responses are important in cancer care because "patients have less anxiety and depression and report greater satisfaction and adherence to therapy," the researchers noted. The study found that female patients were more likely to disclose painful emotions to female oncologists. In addition, younger oncologists and those who rated their orientation as more socioemotional than technical were more likely to respond with empathic statements.

"Oncologists and patients need to work to create an alliance conducive to patients expressing their emotions," the researchers suggested. Although the oncologists expressed high levels of confidence in addressing emotions, they may need more training to recognize emotions and to learn how to respond to patient concerns. "Many empathic opportunities were indirect and patients may be more satisfied if they can learn how to express their emotions more directly so that oncologists can respond appropriately," the authors noted.

Biomarkers Linked to DCIS Outcomes

Ductal carcinoma *in situ* (DCIS), where abnormal cells are found in the lining of a breast duct, is usually treated with surgical lumpectomy, followed by radiation, chemotherapy, a combination of the two, or surveillance. Most women undergoing these treatments will not experience a recurrence, but in 15 to 30 percent of women, a new tumor will develop within 10 years, and about half of these will be invasive breast cancers. To help clinicians determine whether DCIS is likely or unlikely to follow this course, researchers at the University of California, San Francisco, and the Bay Area Breast Cancer Specialized Program of

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Research Excellence (SPORE) have identified biomarkers associated with invasiveness. Their results appear in the November 12, 2007, *Cancer Cell*.

Using lumpectomy samples from 70 women who were diagnosed with DCIS and then followed for more than 10 years (180 months), the researchers looked at several markers associated with stress-induced senescence or proliferation. They compared the profiles of these markers in women whose DCIS did not progress to those in women for whom the DCIS did progress.

The results showed that in samples containing proliferating cells identified using Ki67 proliferation marker, overexpression of stress-activated p16 and/or COX-2 proteins reflects abnormal response to cellular stress and predicts subsequent tumor events within the first decade after the initial DCIS diagnosis. Low expression of Ki67 (regardless of the p16 and COX-2 status) usually indicates favorable prognosis. Other findings include observation of post-transcriptional rather than transcriptional regulation of COX-2 expression in a subset of HER-2-positive tumors.

The authors conclude that when tissue shows stress activation and deregulation of p16 and Rb signaling, this "may represent a defining signature of basal-like carcinogenesis that can be assayed [before] the development of invasive disease," with opportunities for prevention years before an invasive tumor actually occurs.

Older Breast Cancer Survivors Less Likely to Adhere to Follow-Up

Two new studies have revealed that older breast cancer patients who are more likely to experience recurrence are less likely to undergo recommended follow-up mammography and adhere to prescribed medications. In the clinical trials that lead to treatment and follow-up guidelines for breast cancer, older women are usually underrepresented due to eligibility criteria or comorbid conditions. But two recent community-based studies that focused on breast cancer survivors over the age of 65 addressed specific questions related to the behavior and outcomes of this group, using participants in health systems that collaborate through the NCI-funded HMO Cancer Research Network (CRN).

The first study, published online December 1, 2007, in the *Journal of General Internal Medicine*, looked at surveillance mammography among women who were diagnosed with stage 2 or earlier breast cancer. Most of the 1,762 women in the study were older than 70. After 4 years of follow-up, the study showed that women at the highest risk of recurrence—those who were diagnosed at stage 2 and those who had breast-conserving surgery without radiation—were the least likely to have recommended mammograms. Other factors associated with this trend included age older than 80 and nonwhite ethnicity.

The second study, published ahead of print in the *Journal of Clinical Oncology* on December 10, 2007, reviewed tamoxifen use by 961 women during a 5-year follow-up period after treatment. The results showed that 49 percent of these women stopped taking tamoxifen within this time. Women over the age of 75, as well as those who had comorbid conditions, breast-conserving surgery without radiotherapy, and those in whom tumor estrogen-receptor status was unknown, were the most likely to discontinue use. Reasons for stopping in the first year most often related to side effects of the drug.

In both papers, the authors noted that by understanding the risk of nonadherence to recommended follow-up procedures, clinicians may be able to tailor their care of this patient group.

More information on collaborative research opportunities and NCI's CRN resource can be found at http://crn.cancer.gov/about/work.html.

Trial Shows Some Benefit of Adjuvant Chemo for Early Colorectal Cancer

A large European trial designed to determine the value of adjuvant chemotherapy after surgery for stage II colorectal cancer has found that patients receive "small but definite benefit" in both survival and risk of recurrence, say researchers at the University of Birmingham in England.

The QUick And Simple And Reliable (QUASAR) Trial Collaborative Group, led by Dr. Richard Gray, reported results on 3,239 patients after 5.5 years median follow-up in the December 15, 2007, *Lancet*. Compared with observation alone, patients receiving chemotherapy had an 18-percent reduction in risk of death, which, in a population whose mortality rate is about 20 percent, conferred an absolute reduction of 3.6 percent at 5 years. The 22-percent reduction in risk of recurrence occurred almost completely in the first 2 years, and then leveled off.

"Chemotherapy seems to prevent a proportion of recurrences and deaths rather than just delaying them," wrote the authors, "which makes the life-years gained more substantial, especially for younger patients."

Drs. David Cunningham and Naureen Starling of the Royal Marsden Hospital in Surrey wrote in

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A Closer Look

A Kinder Cut: Advances in Surgery for Head and Neck Cancer

Before the development of chemotherapy, radiation therapy, and targeted treatments for cancer, there was surgery. And today, the physical removal of cancerous tissue remains a cornerstone of treatment for most tumor types.

But cutting into the body comes with many risks, and it leaves its mark. In parallel with their colleagues working on the systemic treatment of cancer, academic surgeons have been performing research to improve the outcomes of surgical oncology, attempting to minimize damage, maximize effectiveness, and improve reconstruction of damaged tissue.

Smaller Surgeries

One area of the body that has been a focus of experimental surgery is the head and neck. The first large advance in surgery for head and neck cancer came in the 1970s, with the development of techniques that allowed surgeons to begin operating around the area's fragile structures. But these surgeries were incredibly invasive procedures.

For example, for tumors at the base of the skull, "Traditionally…they would have to open up the face and even maybe remove part of the face to get at these tumors, or come in from above, opening up the skull and moving the brain aside," explains Dr. Carter Van Waes, chief of the Head and Neck Surgery Branch at the National Institute on Deafness and Other Communication Disorders. "It was successful in curing many patients or…palliating the disease, but the functional and aesthetic outcomes were short of what people desired."

The next surgical revolution came in the 1980s and 90s, with the rise of minimally invasive endoscopy applied to head and neck surgery. The endoscope allows surgeons to operate through existing openings, such as the nose and mouth, or through relatively small incisions, potentially reducing surgical morbidity.

Recently, the Southwest Oncology Group tested endoscopic transoral (through the mouth) surgery in a phase II clinical trial for patients with early-stage laryngeal cancer. Although the trial did not have a standard, open-surgery control group, says senior study investigator Dr. David Schuller from Ohio State University, "Subjectively we're seeing absolutely no difference in terms of survival outcomes, but certainly are impressed with the decreased morbidity, the decreased length of hospital stay, and the decrease of blood loss. So we're cautiously optimistic.

"If we could continue to use surgical modalities to help us with cytoreduction at the same time that we decrease morbidity—enabling the patients to move on quickly to nonsurgical adjuvant therapies—that's the hope," he continues. Investigators are now experimenting with robotics-assisted endoscopic surgery in the head and neck region, to assess its feasibility and potentially increased surgical precision in small physiologic spaces.

Putting the Pieces Back Together

Of significant importance to patients undergoing surgery for a tumor in the head or neck region is how the operation will affect their quality of life—their ability to speak, swallow, eat, and breathe, as well as their appearance.

Fortunately, reconstructive surgery for the head and neck region has also made great strides in the past 20 years. Before modern tissue transfer techniques became possible, simple skin and nonvascular bone grafts were used to close a remaining defect and prevent infection. But these techniques were not adequate to restore normal appearance, and in the case of bone grafts, were often reabsorbed by the body.

An important advance in surgical reconstruction came with the development of pedicled (attached) regional flap transfer, which allowed surgeons to cut a piece of tissue from a nearby structure (such as a chest muscle) and move it, still attached to its blood supply, to the site of the surgical defect.

Though a vast improvement over nonvascular grafts, this technique was limited to nearby donor tissue. Additionally, the flaps could have problems healing, particularly from tension caused by the attachment to the donor site or damage to the recipient site from radiation therapy. These problems were addressed by the development of free tissue transfer, in which microvascular surgeons remove a piece of muscle, bone, or both, from elsewhere in the body, along with the associated blood ves-

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sels, and reattach those blood vessels at the transplant site.

"More and more head and neck surgeons have become trained in microvascular techniques, and I think, once a critical mass of microvascular surgeons was available to perform these procedures and analyze the effect of these reconstructions—showing their superiority in many instances—that really allowed it to become standard [care]," explains Dr. Theodoros Teknos, chief of Head and Neck Oncologic Surgery at the University of Michigan.

Free-flap transfer can also be combined with dental and facial prosthetics, to include artificial ears, eyes, teeth, or other body parts and provide a more natural appearance for patients.

Looking to the future, says Dr. Teknos, "The next big phase in reconstruction is going to be tissue engineering." To avoid the donor-site damage that can be caused by harvesting muscle or bone for free-flap transfer, and to provide more personalized reconstructions, investigators are experimenting with growing custom bone, using adult stem cells, or protein or gene therapy.

Recently, investigators in Germany succeeded in growing a new jaw bone for a man who had undergone an extensive tumor surgery. The researchers filled a custom mesh cage with bone mineral blocks, bone marrow containing hematopoietic stem cells, and bone morphogenic protein and implanted it into the patient's back muscle, creating a new piece of custom-fitted bone with a healthy blood supply that they successfully transferred to the jaw.

For both future ablative and reconstructive advances, participation from all the associated specialties will remain essential. "Bringing together the thought leaders from all over the country, from all of the disciplines…not just the therapeutic, but also the rehabilitative and the quality-of-life expertise…I think that's what's going to accelerate the productivity in clinical research," concludes Dr. Schuller. ◆

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genotype) were four times as likely to develop the cancer as patients with the *A/A* genotype. These associations remained significant even after adjusting for age, sex, race, and cause and severity of cirrhosis. The researchers found correspondingly higher EGF and phosphorylated EGF receptor (EGFR) levels in the liver and serum of patients with the *G/G* genotype.

Collaborators at the Hôpital Paul Brousse in France provided genetic data for a validation study, from 121 white patients with alcoholic cirrhosis seen between 1993 and 2006. Forty-four of those patients later developed HCC.

As in the Massachusetts population, patients with the *G/G* genotype were significantly more likely to develop HCC—in this case almost three times as likely—than patients with the *A/A* genotype.

Although "prospective studies examining larger populations of patients… and the application of these observations to ethnic minorities," are needed, explain the authors, they remain intrigued by the possibilities for HCC screening and prevention.

"Identification of molecular markers associated with an increased risk of hepatocellular carcinoma would better define populations at highest risk… and may additionally define important therapeutic targets for prevention and treatment," they state. "Our findings… provide rationale for examination of the EGF-EGF receptor pathway as a novel target for chemoprevention in humans."

Dr. Tanabe's laboratory has begun preliminary work to look for a chemoprevention agent nontoxic enough for long-term use. "We're already looking at the EGF-EGFR pathway using *in vitro* transformation models to screen potentially clinically useful compounds that would inhibit transformation, and are also developing similar animal models. Setting up those platforms for drug discovery and drug testing could go in parallel with a confirmatory study…It happens to be that a SNP modulates serum EGF levels [in this study], but of course there may be many, many other things that modulate EGF levels," he concluded. ◆

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incorporated into the RCDC system and extended to the proper coding of cancer research across the NIH.

We will keep the community informed of activities and progress in this critically important area. We want to reinforce the importance NCI places on being as open and accountable as possible to the public, as mandated in the National Cancer Act. We firmly believe, however, that this activity must be led by NCI. ◆

Dr. John E. Niederhuber
Director, National Cancer Institute

Spotlight

Genome Scans for Cancer: What's Next?

Scanning the human genome for genetic variants involved in common cancers began to pay dividends in 2007, and the trend is likely to continue as more large studies involving new types of cancer report their results in the coming year.

For the first time, researchers have been discovering and validating genetic variants associated with common cancers such as breast, colon, and prostate. The genetics of these diseases have been exceedingly difficult to dissect, but that is starting to change, thanks to new technologies and the use of large and carefully selected patient populations.

"We're starting to unlock the genetic secrets of common, complex diseases," said Dr. Teri Manolio of the National Human Genome Research Institute, who organized a seminar on genome-wide association studies last summer. "The big lesson in cancer is that you find strong signals in parts of the genome where there aren't any known genes."

Indeed, much of the excitement surrounding genome scans comes from discoveries in places where no one had thought to look, such as a region of chromosome 8 called 8q24. The region has no known genes. But when three prostate-cancer scans published on the same day last year pointed to 8q24, it became a research priority almost overnight.

"The current excitement in the field is about what the scans will tell us about the biology of cancer," said Dr. Thomas Sellers of the Moffitt Cancer Center, who is collaborating on genome scans for ovarian cancer. "It's hard for patients to get excited about that, but this is important for progress in research and developing treatments."

Scans are underway, for instance, to find variants underlying individual differences in cancer risk, drug response, the risk of relapse, and second cancers. And as technology improves and the basic strategy is refined, scans will likely be used in new ways.

In addition to breast, colon, and prostate cancers, scans were reported last year for acute lymphoblastic leukemia. The studies largely involved patients of European descent and will need to be repeated in African and Asian populations. Scans are underway or nearing completion for lung, pancreatic, ovarian, and bladder cancers, to name a few.

A substantial number of these studies will be published for additional types of cancers in 2008, predicted Dr. David Hunter of the Harvard School of Public Health and a leader of NCI's Cancer Genetic Markers of Susceptibility (CGEMS) program. "One can expect that new, previously undiscovered associations will be found, and that should help us learn more about the inherited causes of these cancers."

For prostate, colon, and breast cancers, the story is far from over. Researchers are racing to explain associations among all three cancers and 8q24. The region may contain DNA sequences that regulate cancer-related genes, but further evidence explaining the plausibility of the findings has yet to be published.

"Something mysterious is going on in 8q24, and we are having difficulty putting the data in a rational context," said Dr. Kari Stefansson of deCODE Genetics, which first linked the region to prostate cancer in 2006. Nonetheless, he expects an answer by spring.

"Genome scans are the best tool we've ever had to pinpoint the genetic causes of disease," Dr. Stefansson added. "Never in history have we had anything that comes close. They are not perfect, but the ability to look at hundreds of thousands if not millions of variable regions of the genome at the same time is remarkable."

Scans often involve thousands of subjects. Success depends in part on having relatively homogeneous patient populations and matched comparison groups. DNA from both groups is screened for variants found more often in the affected group. Results are then tested in additional patient

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populations to confirm associations and avoid false-positives.

Most of the variants reported to date have modest effects on disease risk and would not be used in the clinic. With the next generation of genome scans, researchers will begin to focus on assembling panels of common risk variants.

"The goal is to quickly transition from discoveries in single studies to discoveries in several studies, and to put together strong robust findings so that researchers can test 10 to 20 common variants," said Dr. Stephen Chanock, of NCI's Division of Cancer Epidemiology and Genetics (DCEG), who directs its Laboratory of Translational Genomics.

"We are most excited about the opportunity to put them all together because we know that is where we want to be," said Dr. Chanock. Collaborative studies across the globe will be needed to achieve this goal, and efforts toward this end are underway.

By combining scans for the same cancers, it should be possible to look at subtypes of disease to see if there are specific genetic factors that one wouldn't see when looking at the total group, said Dr. Robert Hoover, also of DCEG and a leader of CGEMS.

Meanwhile, researchers are testing associations in their own study populations. Of particular interest is the increased risk of prostate cancer in African American men. "The initial scans were largely done in white populations, and we're trying to see whether the effects are the same in men of African descent," said Dr. Timothy Rebbeck of the University of Pennsylvania.

Another application is to use scans to find protective genes. One such variant has been found for breast cancer, and others may follow. An international consortium is planning to screen women with mutations in the *BRCA2* gene for genetic variants that may cause some of these women to develop breast cancer at an early age and others not.

"If we find a genomic pattern that is protective in the genetic background of *BRCA2* mutations then we will see if this result is generalizable," said Dr. Kenneth Offit of Memorial Sloan-Kettering Cancer Center, who is leading a study by CIMBA (Consortium of Investigators of Modifiers of *BRCA1* and *BRCA2*).

Genome scans may indirectly lead to environmental factors involved in cancer. For instance, genes that are more strongly associated with breast cancer in women who use hormones than in nonhormone users may mediate the effects of exposure to hormones. Understanding the biological pathways involved could lead to safer uses of the therapy.

Epigenetic changes to DNA, which regulate gene activity without altering DNA sequence, also play a role in cancer. Understanding the interactions among genetic, environmental, and epigenetic factors on cancer represents an enormous challenge, and researchers stress that genome scans are merely the beginning.

In fact, genome scans often do not reveal the precise stretch of DNA responsible for an association, so more work is needed to pinpoint it. Then, functional studies are needed to truly understand the source of the association.

"Results of scans should be replicated many times by multiple groups before reaching firm conclusions or changing therapy based on the findings," cautioned Dr. William Evans of St. Jude Children's Research Hospital, who has collaborated on leukemia scans and used this approach in pharmacogenomic studies.

Dr. Mary Relling, also at St. Jude, added: "We need to be honest with the public and with our funding agencies that this process is going to be hard and will be done over decades." Nonetheless, she is optimistic and believes that genome-wide approaches are important because they may reveal factors that might otherwise be missed.

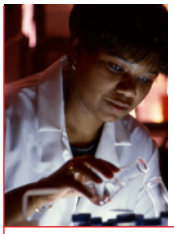
Dr. Relling is using scans in combination with other tools to study variation in drug response and toxicities among children with leukemia. And in the field of pharmacogenomics generally, many scans are underway using patient cells.

"Just as the use of scans for identifying risk factors in common diseases has exploded on the scene, you're going to see an echo of that explosion in research on variation in drug response," said Dr. Richard M. Weinshilboum of the Mayo Clinic, a former chair of the Pharmacogenetics Research Network. "Tune in next year for the results."

Researchers have seen "the first light of genetic variants associated with common diseases that we had never thought of before," said NCI's Dr. Chanock, who is a leader of CGEMS. "The excitement comes from seeing that our strategy works and that the approach is sound." The information from these studies will be used in many ways, including some that are not yet apparent.

"We are putting the CGEMS results out there and counting on people to look at the information from many different perspectives," Dr. Chanock said. ◆

By Edward R. Winstead



Featured Clinical Trial

Stress Management Therapy for Chemotherapy Patients

Name of the Trial
Randomized Study of Stress Management Therapy in Patients Undergoing Chemotherapy for Cancer (MCC-0501). See the protocol summary at http://cancer.gov/clinicaltrials/MCC-0501.

Principal Investigators
Dr. Teletia Taylor, Howard University, and Dr. Susan McMillan, University of South Florida


Dr. Teletia Taylor

Why This Trial Is Important
Undergoing treatment for cancer may be one of life's most stressful experiences. Patients scheduled for chemotherapy may wonder how they will deal with its well-known side effects, such as nausea, vomiting, hair loss, and fatigue. These and other uncertainties can lead to overwhelming stress, which can reduce a patient's quality of life and, possibly, interfere with their recovery.

In this study, patients with newly diagnosed cancer who are scheduled to undergo chemotherapy will be randomly assigned to one of two groups. One group will receive standard psychosocial care along with stress management training, while the other will receive standard psychosocial care alone. The self-administered training will consist of multimedia information and instructions about three stress management techniques: progressive muscle relaxation and guided imagery, abdominal breathing, and coping skills.

Hispanic/Latino patients reportedly experience a disproportionately higher level of suffering from cancer and treatment-related stress. This is due, in part, to a lack of culturally relevant resources in Spanish. This study uses culturally sensitive self-education tools in both English and Spanish that are linguistically appropriate and incorporate Hispanic/Latino cultural beliefs.

"The adverse effects of chemotherapy on quality of life are well documented," said Dr. Taylor. "Stress management techniques have been shown to have beneficial effects on nausea, vomiting, and emotional distress before the administration of chemotherapy as well as in the days following chemotherapy.

"The primary objective of this study is to determine whether a self-administered stress management intervention, previously found to be beneficial to primarily non-Hispanic chemotherapy patients in a single clinical setting, is effective in improving quality of life and decreasing psychological distress (anxiety and depression) in Hispanic and non-Hispanic patients receiving cancer chemotherapy in multiple community clinical settings. We have met our accrual target for non-Hispanics, so the trial is now open only to Hispanic patients," Dr. Taylor added.

For More Information
See the lists of eligibility criteria and study sites at http://cancer.gov/clinicaltrials/MCC-0501 or call the NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237). The toll-free call is confidential. ◆

An archive of "Featured Clinical Trial" columns is available at http://cancer.gov/clinicaltrials/ft-all-featured-trials.

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an editorial that the QUASAR results do not fully resolve all of the issues in this population, and that "identification of patients most likely to benefit from therapy remains important." Subgroup analyses are underway.

Better information about these groups, they wrote, may help patients and physicians assess the risk/benefit ratio among the three options currently in use: fluorouracil with oxaliplatin, fluoropyrimidine, or observation. These newer drugs and combinations have largely supplanted the drugs tested in QUASAR. ◆

Funding Opportunities

For a complete listing of current NCI funding opportunities, please go to the HTML version of today's *NCI Cancer Bulletin* at http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_010808/page8. ◆

Notes

National Quitline Celebrates One Million Calls

On December 30, 2007, 1-800-QUIT-NOW received its one millionth call. Since its inception in 2004, the national, toll-free number providing free help quitting tobacco use has routed one million callers to their respective state quitlines—telephone-based services that help smokers quit through counseling, information, self-help materials, and in some instances, nicotine replacement therapy. Over the past 3 years, quitlines have become an integral part of many smokers' cessation efforts.

1-800-QUIT-NOW was developed by the National Network of Tobacco Cessation Quitlines, the North American Quitline Consortium, the Centers for Disease Control and Prevention, and NCI to help tobacco users quit. Additional information on quitting smoking can be found at http://smokefree.gov/; information on smoking and cancer is available at http://www.cancer.gov/cancertopics/smoking.

Revised OSPA Snapshots Available

NCI's Office of Science Planning and Assessment (OSPA) recently updated and released a set of 22 disease site-specific "Snapshots," including a new one on liver and bile duct cancers. The concise one-page, double-sided documents provide a snapshot of trends in disease incidence and mortality, NCI's investment by fiscal year, examples of current relevant NCI initiatives, and selected research highlights. To view or download the snapshots, go to http://planning.cancer.gov/disease/snapshots.shtml.

Cancer in the Developing World Seminar Now Available Online

The joint NCI/American Society of Clinical Oncology (ASCO) Science Writers' Seminar on "Cancer in the Developing World" is now available at www.asco.org/presscenter.

The seminar, held on December 20, 2007, featured internationally recognized experts providing an in-depth, informative look at many issues surrounding cancer in less developed countries, including geographic incidence; survival and mortality trends; the state of cancer prevention, screening, and treatment in less developed countries; perspectives on cancer care from Africa, Asia, and India; major international cancer initiatives in prevention, tobacco control, and palliative care; and ASCO and NCI initiatives to address the global cancer burden.

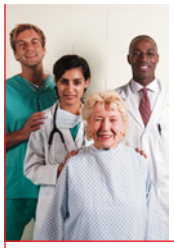
The audio track, slide presentations, bio sketches, and fact sheets from this event are also available through ASCO's online press center. Log on to www.asco.org/presscenter and click on the Meet the Experts link.

A new issue of *BenchMarks* on the Global Burden of Cancer is also available. Go to http://www.cancer.gov/newscenter/benchmarks-vol7-issue2. ◆

Cancer.gov Update

Resources for DCIS Researchers

NCI's Division of Cancer Control and Population Sciences launched a new Web page on ductal carcinoma *in situ* (DCIS) research resources in November 2007. The need for this Web page for DCIS investigators was identified at a workshop hosted by NCI in February 2007 on Strategies for Integrating Tumor Biology and Population Sciences to facilitate more rapid application of basic science discoveries into population-level research. DCIS, also called intraductal carcinoma, is a form of noninvasive breast cancer. In some women, DCIS lesions will progress to invasive cancer, although at present, researchers cannot reliably identify these high-risk patients. The new Web site provides information about DCIS, including summaries and presentations from the 2007 workshop, research resources, and opportunities for collaboration. The site also provides information on key priorities in DCIS research as well as information on relevant research funding opportunities. ◆



Cancer Center Profile

Oregon Health & Science University Cancer Institute

Director: Dr. Brian J. Druker • 3181 S.W. Sam Jackson Park Road, CR 145, Portland, Oregon 97239 • 503-494-1617 • Web site: http://www.ohsucancer.com/

Background

From its inception in 1992, the Oregon Health & Science University (OHSU) Cancer Institute was conceived as a resource that would draw on its strengths as part of an academic health center and research powerhouse. In 1997, the OHSU Cancer Institute became the only NCI-designated Cancer Center in Oregon. Dedicated to reducing the cancer mortality rate in Oregon by connecting with existing statewide physician networks, the OHSU Cancer Institute's mission is to translate discoveries into better ways to diagnose, prevent, and treat cancer.

The institute is known worldwide for leadership in molecularly targeted therapies, including the most celebrated cancer discovery in a generation: the drug Gleevec (imatinib). Gleevec was developed by Dr. Brian J. Druker, who is JELD-WEN Chair of Leukemia Research and director of the OHSU Cancer Institute. Recently elected to the National Academy of Sciences, Dr. Druker also is a Howard Hughes Medical Institute Investigator.

Research Activities

With more than 300 researchers and more than 200 open clinical trials, the OHSU Cancer Institute is the region's primary hub for cancer clinical trials. The institute's research program focuses on four areas: cancer biology; hematologic malignancies; solid tumors; and cancer prevention and control. The institute includes oncology researchers from the OHSU schools of medicine, nursing, and dentistry; the OHSU Casey Eye Institute; and OHSU Doernbecher Children's Hospital. Many OHSU clinical trials have led to treatment advances in prostate, breast, and colon cancers; leukemia; lymphoma; gastrointestinal stromal tumors; and other malignancies. For example, OHSU-led research established colonoscopy as the gold standard for early detection of colon cancer. In 2006, OHSU was one of 12 institutions that received the NIH Clinical and Translational Science Award.

Patient Care Specialties

Each year OHSU Cancer Institute clinicians oversee more than 3,500 inpatient admissions and 35,200 outpatient visits. Multidisciplinary teams of medical oncologists, radiation oncologists, surgical oncologists, nurses, pharmacists, physical therapists, social workers, and nutritionists create a customized treatment plan for adult and pediatric patients. Renowned for its leukemia and prostate cancer care programs, the OHSU Cancer Institute is the only resource in the region for allogeneic bone marrow transplant, and it offers unique expertise in complex sarcoma, head and neck, pancreatic, liver, and neurosurgical cancer treatment. The institute's Department of Radiation Medicine offers state-of-the art technologies, including the only Calypso image guidance radiation system in the region, while ongoing research in stereotactic body imaging promises more precise radiation treatment options.

Other Notable Programs

The OHSU Cancer Institute's Adolescent and Young Adult Oncology Program, one of only a handful in the nation, facilitates services for the 15- to 40-year-old cancer population, including screening for clinical trials, fertility counseling, social support and networking, rehabilitation, and other services. The Colorectal Cancer Assessment and Risk Evaluation Clinic brings together health professionals from medical genetics, oncology, gastroenterology, surgery, pathology, nutrition, and social work for individualized treatment; the associated statewide colorectal cancer registry captures genetic information. The Breast Health Education Program trains clinicians throughout Oregon on clinical breast examination and provides breast health education to patients. The institute's Cancer Prevention and Control Program connects scientists with national databases to analyze cancer trends. ◆