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FDA Advisory Committee Suggests Changes to ESA Use

An advisory committee to the Food and Drug Administration (FDA) has recommended that the agency consider adding new restrictions on the use of antianemia drugs in cancer patients with chemotherapy-induced anemia. The advisory committee's May 10 meeting was the most recent stage for debate about what has become a matter of significant concern: whether use of a blockbuster class of drugs that reduces the need for blood transfusions in the estimated 450,000 cancer patients who receive them annually could be putting them at a greater risk of death.

None of the recommendations offered by the agency's Oncologic Drugs Advisory Committee (ODAC) were highly specific. The committee did, however, advise FDA to evaluate all available and forthcoming data to determine if the use of these drugs, often called erythropoiesis-stimulating agents (ESAs), should be limited in patients with certain tumor types; whether a specific hemoglobin level to trigger the drugs' use in asymptomatic patients should be established; and whether limits should be placed on their use within a certain time frame after chemotherapy is completed. *(continued on page 2)*

Director's Update

Celebrating Women's Health

As we are all aware, last Sunday was Mother's Day. Fittingly, it was also the first day of National Women's Health Week, an annual opportunity to educate women about important health screenings and to encourage them to take advantage of every opportunity to prevent diseases like cancer.

Now in its eighth year, this federally sponsored event particularly emphasizes mammography, which—along with adjuvant chemotherapy—was responsible for a 24-percent reduction in breast cancer mortality between 1990 and 2000, according to an NCI-funded study published in 2005.

As the recently released *NCI Women's Health Report* demonstrated, NCI and the cancer community have much to be proud of in breast cancer research and beyond. Yet we also have a tremendous amount of work to do. Articles in this week's issue touch on both accomplishments and needs.

We are continually striving to bolster the effectiveness of breast screenings. An NCI-funded study, for example, demonstrated that digital mammography may be superior to standard film mammography for women with *(continued on page 2)*

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ODAC Chair Dr. S. Gail Eckhardt, from the University of Colorado Health Sciences Center, stressed that the committee should not be looking to return to the "dark ages" when transfusions of red blood cells were the primary supportive care options for anemic cancer patients. Rather, she said, the goal was to determine how to "move forward" given the safety concerns about ESAs prompted by several clinical trials completed over the last 4 years.

The results of one of those trials were presented just 3 weeks ago at the American Association of Cancer Research (AACR) annual meeting. The nearly 1,000-patient phase III, double-blind, randomized, placebo-controlled clinical trial—called the "103 study"—showed an increased mortality risk in cancer patients with a variety of tumor types who were given the ESA darbepoetin alfa (Aranesp), one of two FDA-approved ESAs manufactured by Amgen.

In early March, based largely on the 103 study results and some preliminary data from a Danish trial called DAHANCA 10 that suggested safety concerns, the FDA, among other measures, issued a public health advisory and added a new "black-box" warning to the ESAs marketed in the United States.

Of the clinical trials that have shown an increased mortality risk, only the 103 study's protocol called for using ESAs to achieve the hemoglobin level called for on the drugs' labels, 12 g/dl, explains the trial's lead investigator, Dr. John Glaspy from the UCLA Jonsson Comprehensive Cancer Center. The other ESA clinical trials that have shown a mortality risk were all designed to achieve hemoglobin levels in the 13 to 15 g/dl range—what Amgen representatives referred to as "beyond anemia correction" studies; in two of the trials, patients did not even have to be anemic to enroll.

The 103 study, which did not have survival as its primary endpoint, was also different from the other trials because it involved patients whose anemia was associated with their underlying cancer, for which no benefit of an ESA has been established.

"It's very appropriate to be cautious and do the additional work to run this down, because it's a patient safety issue," says Dr. Glaspy, who also spoke during the meeting on Amgen's behalf. "But I believe that at the end of the day, when used the way we've been using these drugs in oncology, they will be safe."

Amgen representatives also presented preliminary data from the recently completed, 600-patient "145 study," a randomized, double-blind trial in which patients with small-cell lung cancer were treated to a hemoglobin target of 13 g/dl. Patients treated with darbepoetin alfa had equivalent overall and progression-free survival compared with those given placebo.

Although the design and conduct of most of the trials that have exhibited a safety concern have come under intense criticism, says Dr. David P. Steensma from the Division of Hematology at the Mayo Clinic, "I think we have enough evidence now to suggest there is a problem."

During the meeting, ODAC members expressed dismay at the lack of simple trials involving ESAs with a progression-free or overall survival endpoint and the lack of data on ESAs' effects on tumors. They also criticized the direct-to-consumer TV ads for ESAs that suggest they improve problems like fatigue and quality of life, which are unapproved indications in the United States. ◆

By Carmen Phillips

(Director's Update continued from page 1)
dense breasts. More recently, it was shown that adding an MRI scan to the standard diagnostic workup following a diagnosis of breast cancer can detect nearly all contralateral breast cancers missed by mammography.

Unfortunately, as the results of an NCI-led study released just yesterday reveal, progress does not preclude the need for continued diligence. The study showed a recent decrease in mammography rates, a drop that includes women most likely to benefit. National Women's Health Week provides an ideal opportunity to remind women about the potentially life-saving importance of regular cancer screenings including colonoscopy, skin exams, and Pap tests.

We are also well aware that the leading cause of cancer deaths in women is lung cancer—a source of significant concern and a high-priority issue for NCI. The NCI lung cancer Specialized Program of Research Excellence at the University of Pittsburgh, for instance, is investigating whether estrogen receptors may play a role in women being more prone than men to getting a more aggressive form of lung cancer.

One of the most exciting advances in women's health was the approval last year of the HPV vaccine Gardasil. Recently released data suggest that Gardasil and another investigational HPV vaccine are safe and confer long-term protection against these HPV types. Meanwhile, the NCI researchers whose work led to the development of these first-generation vaccines are collaborating with researchers from Johns Hopkins University on a second-generation vaccine intended to protect against more HPV types.

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Cancer Research Highlights

Recent Drop in Mammography Rates Causes Concern

The drop in mammography rates in the United States in recent years is cause for concern because it could contribute to a future rise in breast cancer deaths, according to an analysis of data from representative national surveys published early online in *Cancer*.

Scientists from NCI's Division of Cancer Control and Population Sciences (DCCPS), led by Dr. Nancy Breen, examined data from the Centers for Disease Control and Prevention's National Health Interview Surveys (NHIS) and found a decline in mammography screening in 2005 compared with 2000—from 70 percent to 66 percent. After many years of increases in mammography use, "[t]his report establishes for the nation what has already been observed in some local data. It confirms that use of mammography may be falling. Although small, this decline is cause for concern, as it signals a change in direction."

Mammography screening rates were lower in 2005 than in 2000 for nearly all the groups of women examined. "The largest significant declines were among women who have traditionally used mammography at high rates, including the 50–64 age group, those with higher incomes, and women aged 40–64 with private, non-HMO insurance coverage," the DCCPS investigators noted.

When screening rates drop, women with breast cancer will be diagnosed later, resulting in a short-term drop in incidence, they add. "Consequently, we are concerned that some of the observed decline in incidence may be due in part to the leveling off and reduction in mammography rates." The trend "may presage a future increase in mortality from breast cancer" from later detection of more advanced disease. "If future NHIS data continue to show a decline in mammography use, then we as a nation need to be prepared to address it," the NCI scientists concluded.

The recent decline in breast cancer incidence rates was examined in a separate study published May 3 in *Breast Cancer Research*. Scientists from the American Cancer Society, led by Dr. Ahmedin Jemal, examined data from NCI's Surveillance, Epidemiology, and End Results (SEER) program.

"Two distinct patterns are observed in breast cancer trends," they reported. The downturn in incidence rates in all age groups above 45 years coincides with a plateau in mammography use, which typically reduces incidence rates "due to a reduced pool of undiagnosed cases." The sharp decrease in incidence from 2002 to 2003 that occurred in women 50 to 69 years old who predominantly, but not exclusively, had ER-positive tumors may reflect the early benefit of the reduced use of hormone replacement therapy. A number of investigators within NCI-funded initiatives are now examining the contribution of recent changes in screening and hormone therapy to breast cancer trends.

HPV a Risk Factor for Oropharyngeal Cancer

A new epidemiological study led by researchers from Johns Hopkins University implicates human papillomavirus (HPV) exposure and infection as strong risk factors for oropharyngeal cancer. The results from the case-control study, published in the May 10 *New England Journal of Medicine*, show that HPV exposure and infection increase the risk of oropharyngeal squamous cell cancer independently of tobacco and alcohol use, two other important risk factors for the disease.

The investigators enrolled 100 patients with newly diagnosed oropharyngeal squamous cell carcinoma and 200 control patients in the study. Oral-mucosal and serum samples were colleted from all patients. Tumor samples were also collected from case patients. The investigators analyzed all collected samples for presence of HPV DNA or antibodies that would indicate prior exposure. Personal and medical history information collected included oral hygiene history, sexual history, and lifetime use of marijuana, tobacco, and alcohol.

Researchers found that "the presence of an oral HPV 16 infection was strongly associated with oropharyngeal cancer." HPV 16 is one of the two strains of HPV most often associated with cervical cancer. Past exposure to HPV 16, as measured by presence of antibodies to the virus in serum samples, was also strongly associated with oropharyngeal cancer. Antibodies against HPV 16 were found in 64 percent of case patients but only 4 percent of control patients. Data collected on sexual history "suggest that oral HPV infection is sexu-

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(Highlights continued from page 3)
ally acquired…but we cannot rule out transmission through direct mouth-to-mouth contact or other means," said the authors.

A history of heavy tobacco and alcohol use remained a strong risk factor, but "combined exposure to HPV and heavy tobacco and alcohol use was not additive," they explained. "It is important for health care providers to know that people without the traditional risk factors of tobacco and alcohol use can nevertheless be at risk for oropharyngeal cancer," stated first author Dr. Gypsyamber D'Souza in an accompanying press release.

New Data from HPV Vaccine Trials Available

Results from an average of 3 years of follow-up from the FUTURE I and FUTURE II clinical trials of Gardasil, a vaccine that protects against the two types of human papillomavirus (HPV) that are responsible for 70 percent of all cases of cervical cancer, have been published in the May 10 *New England Journal of Medicine*. Earlier data from the FUTURE II trial led to the FDA approval of Gardasil in June of 2006.

The FUTURE I study randomly assigned 5,455 women between the ages of 16 and 24 to receive either a 3-injection course of Gardasil vaccine or placebo. For women who had not previously been exposed to HPV 16 or 18, the efficacy of the vaccine was 100 percent in "preventing vaginal, vulvar, perineal, and perianal intraepithelial lesions or warts associated with the vaccine-type HPV."

In an intention-to-treat analysis, which included women who had previously been exposed to HPV 16 or 18, the vaccine efficacy was 73 percent against all grades of external anogenital or vaginal lesions and 55 percent against all grades of cervical lesions related to those HPV types.

The FUTURE II study randomly assigned 12,167 women between the ages of 15 and 26 to receive either a 3-injection course of Gardasil vaccine or placebo. For women who had not previously been exposed to HPV 16 or 18, the vaccine prevented 98 percent of high-grade cervical intraepithelial neoplasia related to those HPV types.

In an intention-to-treat analysis, which included women who had previously been exposed to HPV 16 or 18, vaccine efficacy was 44 percent against high-grade cervical disease caused by HPV types 16 or 18. As in the FUTURE I trial, "[v]accination did not appear to alter the course of cervical lesions related to HPV 16 or HPV 18 or of infection present at the time of randomization," explained the authors.

The vaccine reduced the rate of all cervical lesions in all patients regardless of prior HPV exposure, including lesions caused by HPV types not included in the vaccine, by 17 percent. "An interim analysis of vaccine trial data submitted to the FDA showed a disproportionate, but not statistically significant, number of cases of grade 2 or 3 cervical intraepithelial neoplasia related to nonvaccine HPV types among vaccinated women," stated Drs. George Sawaya and Karen Smith-McCune from the University of California, San Francisco, in an accompanying editorial. "Updated analyses of data from these ongoing trials will be important to determine the effect of vaccination on rates of preinvasive lesions caused by nonvaccine HPV types."

Additional reliable information from NCI about HPV vaccines and cervical cancer can be found at http://www.cancer.gov/cancertopics/hpv-vaccines.

Hepatitis C Increases Risk of NHL

A large, retrospective cohort study found that U.S. veterans infected with the hepatitis C virus (HCV) have an increased risk of developing certain lymphomas, according to study results published in the May 8 *Journal of the American Medical Association*.

Dr. Eric Engels of NCI's Division of Cancer Epidemiology and Genetics and colleagues looked at patient records collected from U.S. Veterans Affairs hospitals between 1997 and 2004. Researchers selected 146,394 patients who were diagnosed with HCV infection and 572,293 patients who were not. Researchers matched the two cohorts on age, sex, and baseline visit date and type—inpatient or outpatient.

Patients with HCV infection had a 20- to 30-percent increased risk of developing non-Hodgkin lymphoma (NHL) and a nearly threefold increased risk of developing Waldenström macroglobulinemia—a rare type of NHL. Patients with HCV infection also had an elevated risk of developing cryoglobulinemia—a condition marked by abnormal levels of certain proteins in the blood.

The researchers noted, "Although the clinical significance of these findings is unknown, it is possible that screening of individuals infected with HCV could identify early-stage lymphoproliferative conditions suitable for early intervention strategies, including chemoprevention trials on premalignant disease. Future epidemiological and pathophysiological studies are needed to further explore the relationship between HCV and NHL."

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Spotlight

Do Rare Cancer Cells Have a Tale to Tell?

A somewhat different randomized clinical trial was launched earlier this year in women undergoing their first treatment for metastatic breast cancer. It won't pit a standard therapy against an experimental therapy or a new combination of existing agents, or even an experimental therapy against placebo.

Instead, after a single chemotherapy treatment cycle, participants will undergo a blood test that may help predict whether the chemotherapy is working. Women with test results indicating ineffective therapy will then be randomized to either continue on their current therapy until evidence of progression, which is the current standard of care, or to switch immediately to a different chemotherapy regimen.

"Our goal is to study a strategy of treatment, not the drugs themselves," explains the study's lead investigator, Dr. Jeffrey Smerage from the University of Michigan Comprehensive Cancer Center. "We want to identify early on those patients who will benefit before they suffer significant side effects and toxicity, and increase the likelihood that they'll receive a drug that's active."

The test being used in the NCI-funded clinical trial, which is being led by the Southwest Oncology Group (SWOG), measures the number of tumor cells floating freely among the billions of other cells in the blood, typically called circulating tumor cells (CTCs). Studies in patients with metastatic disease, mostly breast cancer, have found that patients whose CTC count just prior to treatment and in the first few weeks following treatment exceeds a particular threshold—5 CTCs per 7.5 mL of blood—have far shorter progression-free and overall survival than those who have low or no detectable CTCs at those times.

Although the majority and largest of these studies have been conducted in breast cancer, smaller studies involving patients with melanoma, prostate, and colorectal cancer have yielded similar results.

As the SWOG trial demonstrates, researchers are now trying to determine just how much clinically relevant information can be wrenched from these rare cells, including whether they can point the way to more tailored therapies, serve as surrogate markers for response to treatment in clinical trials, or provide new insights into the cause of more than 90 percent of cancer deaths—metastasis.

What exactly are they saying?

Although they are detected in blood samples, CTCs are actually epithelial cells that have escaped into the blood stream. Different techniques have been used to separate CTCs from blood cells, although they generally rely on antibodies that attach themselves to proteins expressed by cancer cells but not by blood cells. After separation, further analyses are performed to confirm that the suspect cells are indeed tumor cells.

Although several companies have developed tests and investigators around the world continue to refine and improve the CTC detection process, in the United States, Immunicon Corporation's CellSearch assay is the only CTC test to receive FDA clearance to monitor patients with metastatic breast cancer; several studies described in this article used the CellSearch system and were funded at least in part by Immunicon.

Even with some of the optimism surrounding CTCs, says Dr. George Sledge, from the Breast Care and Research Center at the Indiana University School of Medicine, there currently are serious limits to what measuring CTCs can help accomplish.

"My concerns are not over technology itself, but rather what to do with the result once you have it," he says.

Even though measuring CTCs can predict that a treatment isn't working, Dr. Sledge continues, it doesn't tell oncologists which therapy would do better—a critical need in caring for women with metastatic disease, for which there is no current standard first-line regimen.

The SWOG-led trial is a partial step toward determining whether measuring CTCs can, at least, improve the process by which treatment decisions are made. It is based largely on the results of a prospective clinical trial led by Dr. Massimo Cristofanilli at the University of Texas M.D. Anderson Cancer Center. Initial results from the study, published in 2004 in the *New England Journal of Medicine*, showed that in women with either recurrent or newly diagnosed metastatic

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breast cancer, CTC levels at baseline and 3 weeks follow-up were the most significant predictors of progression-free and overall survival. When a 2005 analysis was confined only to women undergoing first-line treatment, the results were the same.

The available data—including a pivotal study of women treated for metastatic breast cancer published last year—also suggest that CTCs may be a quicker, more accurate predictor of therapeutic effectiveness than the current gold standard, imaging studies typically performed 10 to 12 weeks after treatment to measure whether tumors have grown or shrunk.

The CTC assay was highly reproducible and reliably predicted disease progression, the study found, both of which have been problems in clinical trials that rely on more standard techniques, says Dr. Sledge.

It's unclear whether CTCs may offer the same prognostic insight in patients with operable, early-stage disease. To date, only a handful of studies have been done in this setting, with some promising results reported.

Writing the next chapter

Even if they prove to be of some value in breast cancer, says Dr. Louis M. Weiner, vice president of Translational Research at Fox Chase Cancer Center, it's unknown whether CTCs will be relevant in other cancer types.

Dr. Weiner points to a study in which he was involved that focused on patients with metastatic colorectal cancer, one of only a few studies that have attempted to perform gene expression profiling of CTCs.

"There were very few CTCs in most patients," he notes. "It's beginning to appear that measuring CTCs will be most beneficial in cancer types associated with bone marrow involvement, where you would expect to find more CTCs in the peripheral blood and thus be more accessible to the technology."

So far, CTC-related findings have generated more questions than answers. For example, Dr. Weiner notes, it hasn't been resolved whether CTCs are representative of what's happening at the tumor site, are "adventurous metastasis-prone cells, or…have been kicked out of the tumor neighborhood and are preparing to undergo cell death."

It's questions like these that researchers are now trying to answer, undertaking the task of molecularly characterizing CTCs to determine just what their fate may be or how they differ from cells in the primary tumor. For example, in a small German study of 35 women with stage I to III breast cancer, 12 patients with HER2-positive CTCs had HER2-negative primary tumors.

Other evidence suggests that such HER2 "conversions" aren't uncommon. Such information, says Dr. Sledge, "could potentially be useful in guiding treatment decisions or following the fate of a cell population after completing a form of therapy."

Several studies have suggested that some CTCs have properties associated with chemotherapy resistance and could even be another type of rare cell, a cancer stem cell, which a growing body of evidence indicates may fuel several cancers and be responsible for recurrent disease.

Although there is still much work to do, concludes Dr. Cristofanilli, he is hopeful that CTCs may represent a way "to divide cancer into two different types of disease: more aggressive disease and more indolent disease, so we can start to think about how to develop treatments in a different way." ◆

By Carmen Phillips

(Director's Update continued from page 2)
Along those lines, a study published last week demonstrated that HPV-16 infection was an independent risk factor for oropharyngeal cancer, suggesting the strides being made toward preventing cervical cancer could offer unexpected benefits in another area of cancer prevention—a hallmark of quality research.

Findings from another NCI-supported study led the institute last year to take the rare step of issuing a clinical announcement, advising oncologists about the superiority of intraperitoneal chemotherapy in the treatment of advanced ovarian cancer.

Far too often, though, ovarian cancer isn't detected until it has reached an advanced stage and is far more difficult to treat. In response, NCI has launched the Ovarian Cancer Early Detection Program genetics and screening study to, among other things, identify women at increased risk for developing ovarian cancer and identify and develop highly sensitive and specific tumor markers for the detection of early-stage ovarian cancer.

These are just some examples of how NCI is helping to improve women's health. I'd like to congratulate the NCI Office of Women's Health for its guidance and leadership in helping to advance research on cancers in women. I'd also like to encourage all women who haven't done so recently to use the interactive check-up wizard on the Women's Health Week Web site and make an appointment with their physician to discuss the appropriate screenings they should receive. ◆

Dr. John E. Niederhuber
Director, National Cancer Institute

Special Report

Resistance to Lung Cancer Drug Linked to *MET* Gene

A new cause of drug resistance in patients taking the lung cancer drug gefitinib (Iressa) has been discovered along with a strategy for reversing the resistance.

Researchers have found extra copies of a gene called *MET* in the tumors of some lung cancer patients who stopped responding to gefitinib. Experiments with resistant cells showed that this genetic change—an amplification—can cause the drug to stop working.

Dr. Pasi Jänne of the Dana-Farber Cancer Institute and his colleagues also found that the resistance could be reversed, at least in a cell model. They did this by treating resistant cells with a combination of gefitinib and a compound that inhibits *MET*.

It is not yet clear whether such a combination therapy will work in patients, but an answer should come in the next few years. Many companies are developing agents that target *MET* or its partners, and the first such drugs are in early-stage clinical trials.

The *MET* gene was discovered at NCI in 1984 in the laboratory of Dr. George Vande Woude. It has since been implicated in two dozen cancers.

At least for now, the new results are relevant only to a small subset of lung cancer patients who have mutations in the gene *EGFR*. (About 10 percent of lung tumors have *EGFR* mutations.)

Since the findings were announced last month (and reported online in *Science* on April 26), lung cancer patients have been contacting physicians about the research.

"Patients with cancers involving *EGFR* mutations should be aggressive in searching out clinical trials with novel approaches to treatment if the initial therapies stop working," says Dr. Jeffrey Engelman of Massachusetts General Hospital, the study's first author.

Most lung cancer patients with *EGFR* mutations respond well to gefitinib and a related drug, erlotinib (Tarceva), but resistance usually occurs within 2 years. In half the cases, this happens because of new mutations in *EGFR* or in the genes it controls.

The *MET* gene, however, is not controlled by *EGFR*, nor does it normally interact with gefitinib. So before this study, researchers did not suspect that *MET* played a role in gefitinib resistance.

It now appears that *MET* and *EGFR* may be interchangeable members of the same family of kinase genes. Both produce protein receptors that sit on the cell surface and relay messages to the interior, including signals about growth and proliferation.

"The MET receptor plugs into the same signaling network that the lung cancer cells were using," says Dr. Jänne. In effect, *MET* restores the flow of cancer-promoting signals into the cell.

The question now is how often and under what circumstances the *MET* amplification occurs, says Dr. John Minna of the University of Texas Southwestern Medical Center, who developed the lung cancer cells used in the study.

He agrees that patients whose tumors progress while they are taking gefitinib or erlotinib should be evaluated for participation in one of the clinical trials testing the new inhibitors.

"We need to bring some *MET*-targeted drugs into the clinic and see whether or not they are going to work on these tumors with *MET* amplifications," says Dr. Minna.

Without a cell model of resistance, this research might not have been possible, because tissue samples from patients who develop resistance are extremely rare. After a drug fails, patients rarely have biopsies to determine what caused the failure, yet researchers need these tissue samples to understand how resistance occurs.

"Fortunately, we were able to figure out what was going on in the laboratory and then test the hypothesis on the precious few clinical samples we had," says Dr. Engelman. He obtained 18 samples from patients around the world.

In the future, patients may elect to have biopsies after a drug fails if the resulting information is likely to improve treatment, Dr. Engelman notes. He believes cancer physicians are moving toward an approach to drug resistance pioneered for treating HIV and tuberculosis.

"That means you attack the cancer based on how it would likely become resistant and by doing so you delay resistance and achieve longer term remissions," he says. ◆

—By Edward R. Winstead

A Conversation with… Dr. Vivian Pinn

Dr. Vivian Pinn is associate director for Research on Women's Health and director of the Office of Research on Women's Health at NIH. In 2006, the National Academies Press released a report, Beyond Bias and Barriers, Fulfilling the Potential of Women in Academic Science and Engineering, *which showed that women are underrepresented in these academic fields. In January 2007, NIH Director Dr. Elias Zerhouni convened the NIH Working Group on Women in Biomedical Careers to promote the advancement of women in research both at NIH and in the extramural research community. Dr. Pinn co-chairs the Working Group with Dr. Zerhouni.*

How can the NIH Working Group on Women in Biomedical Careers address concerns raised in the National Academies report?

The Working Group includes representatives from across NIH who are at various career levels: junior and more senior men and women scientists, even a married couple; a post-doc; and institute directors are among the members. Dr. Zerhouni has charged the Working Group to use our insight and creativity to identify factors that contribute to gender bias so that we can change the work culture at NIH and in the extramural community. Two factors identified as barriers in the National Academies report, for example, are the need for mentoring and childcare, so we have subcommittees that are dedicated to these areas, among others. And we will also look at private-sector models that have successfully addressed gender discrepancies in the workplace. Our hope is that these subcommittees will identify the issues that are affecting career advancement for women, identify NIH resources that can assist in overcoming such barriers, and provide recommendations for new programs or modifications of existing ones to address these issues.

What are the immediate goals of the Working Group?

We've established a Web site, Women in Biomedical Careers, where we list the names of the Working Group members, our subcommittees, and the resources related to careers of women in science that have been gathered so far from across NIH and from other organizations and individuals. As programs continue to be identified or implemented, they will be posted on this Web site. Beyond that, we are preparing an interim report for a meeting of the NIH Advisory Committee to the Director in early June. The Working Group is preparing to have initial recommendations in place, or ready to implement, by that time. But June will not be the end of our efforts, as the Working Group plans to continue developing responses to the many challenges for women scientists both at NIH and in the extramural community.

How is your office participating in National Women's Health Week on the NIH campus?

This year our NIH theme is "Caring for the Caregiver: Women as the Portal to Family Health." We chose this theme because women are often the caregivers for an entire family, so by focusing on women, we're also focusing on men's health, elder health, and children's health. Our office is hosting an exhibit on the first floor of Building 31, in the A Wing lobby, which will include information and materials on women's health from across NIH. Additionally, in Conference Room 2 of Building 31 A Wing, we will hold several "Mid-Day for Me" workshops from 12:30–1:30 p.m., because it's time for women as caregivers to give care to themselves, too. Yesterday, Dee Walker, assistant chief of Investigative Services with the Montgomery County Police Department, gave a workshop on women's safety at work and at home. On Wednesday, Rebecca Dunlop, a fitness trainer with the NIH Recreation and Welfare Association, will lead a workshop on exercise and stress reduction at work. And Friday, Maureen Lesser, a nutritionist with the NIH Clinical Center, will lead a workshop on better nutrition at work and at home, as well as bone health. We may repeat these workshops if all who are interested in attending cannot be accommodated by the room.

To learn more about the Office of Research on Women's Health, go to http://orwh.od.nih.gov/. Under the section ORWH Presents: Pinn Point on Women's Health, click on Listen to hear what Dr. Pinn and her guest NIH researchers have to say about current topics in women's health. If you need further assistance on how to use podcasts, go to http://www.nih.gov/news/radio/nihpodcast.htm. ◆

Featured Clinical Trial

Adjuvant Bisphosphonates for Breast Cancer

Name of the Trial
Phase III Randomized Study of Adjuvant Zoledronate Versus Clodronate Versus Ibandronate in Women with Resected Primary Stage I-III Adenocarcinoma of the Breast (SWOG-S0307). See the protocol summary at http://cancer.gov/clinicaltrials/SWOG-S0307.

Principal Investigators
Dr. Julie Gralow and Dr. Robert Livingston, SWOG; Dr. James Ingle, NCCTG; Dr. Carla Falkson, ECOG; Dr. Alexander Paterson, NSABP; Dr. Elizabeth Dees, CALGB; and Dr. Mark Clemons, NCIC-CTG


Dr. Julie Gralow

Why This Trial Is Important
When breast cancer spreads (metastasizes), it often spreads first to the bones. Bone metastases can lead to complications such as pain, fractures, spinal cord compression, bone marrow suppression, and hypercalcemia (abnormally high blood calcium).

Drugs called bisphosphonates have been shown to slow the progression of bone metastases and reduce skeletal complications in women with metastatic breast cancer. Bisphosphonates may also prevent the development of bone metastases in newly diagnosed patients with no evidence of metastasis.

"Breast cancer cells stimulate bone cells called osteoclasts, and these osteoclasts in turn stimulate the growth of breast cancer cells," said Dr. Gralow. "A bisphosphonate called clodronate has been shown to interrupt the relationship between osteoclasts and breast cancer cells in early-stage breast cancer. With this trial, we're comparing clodronate with two newer, more potent bisphosphonates—zoledronate and ibandronate.

"If we can eliminate bone as a safe harbor for breast cancer cells in women who would have experienced bone metastases as the first site of metastasis, we may be able to prevent the spread of breast cancer in these women altogether and save lives. Additionally, we hope to determine which types of breast cancer preferentially metastasize to bone," Dr. Gralow added.

Who Can Join This Trial
Researchers will enroll 6,000 women aged 18 or over whose tumors have been surgically removed and who are receiving, or will receive, standard adjuvant hormonal therapy, chemotherapy, or both. See the list of eligibility criteria at http://cancer.gov/clinicaltrials/SWOG-S0307.

Study Sites and Contact Information
Study sites in the United States are recruiting patients for this trial. See the list of study contacts at http://www.cancer.gov/clinicaltrials/SWOG-S0307 or call NCI's Cancer Information Service toll free at 1-800-4-CANCER (1-800-422-6237). The 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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Study Measures Support Group Use by California Cancer Patients

Nearly one in four people diagnosed with cancer have participated in a support group at some time in their lives, NCI researchers report, though only about half of those did so for problems related to cancer. Nonetheless, cancer survivors' 23.7 percent participation rate was much higher than the 14.5 percent of patients with another chronic illness using a support group.

These results come from an NCI study appearing online May 14 in *Cancer.* Dr. Julia Rowland of NCI's Office of Cancer Survivorship and colleagues say they were surprised to find that only 10.2 percent of cancer patients using a support group were recommended by their physician to do so, given that 78.4 percent of those using such support reported receiving clear and positive benefits.

Both the use of support groups and their perceived benefit varied widely by cancer site. About 26 percent of breast cancer patients had group experience, 78 percent of whom perceived benefit. The highest rate of support group use, 41 percent, was by leukemia and Hodgkin lymphoma patients, with 93 percent of these patients perceiving benefit. Less than 1 percent of lung cancer patients used a group, and those with skin cancer reported the lowest rate of perceived benefit, 35 percent.

The study was conducted using telephone surveys with 9,187 people enrolled in the California Health Interview Survey Complementary and Alternative Medicine. There were 1,844 cancer patients in the survey and 4,951 participants with other chronic health problems. ◆

Notes

OWH Updates Web Site

The NCI Office of Women's Health (OWH) recently added new content to their Research on Cancers in Women Web site.

The site highlights NCI-supported research to understand, prevent, diagnose, and treat cancers that affect women only or cancers with a high impact on women. In addition to disease-specific sections, the site features special topics on AIDS-associated malignancies, cancer health disparities, tobacco prevention and control, and a new section addressing cancer survivorship.

Users can subscribe online to the NCI Women's Cancers listserv to receive notices when new content is posted on the site at http://women.cancer.gov/subscribe.shtml. Users can also help improve the site by providing comments at http://women.cancer.gov/survey.cfm.

Vitamin D Conference Held

On May 7 and 8, more than 100 researchers from around the world attended the meeting "Vitamin D and Cancer: Current Dilemmas/Future Needs." The goal of the conference was to evaluate the scientific evidence related to vitamin D and cancer risk and to identify the research needed to make recommendations for vitamin D intake and/or exposure for cancer prevention. A publication summarizing the proceedings is planned, and a follow-up conference on vitamin D will take place on the NIH campus in September.

LCBG Announces Availability of Samples to Validate Lung Cancer Biomarkers

The Lung Cancer Biomarkers Group (LCBG) has developed a requisite sample resource to validate blood-based biomarkers for the early diagnosis of lung cancer. The LCBG consists of scientists from NCI, the Early Detection Research Network (EDRN), the Lung Cancer Specialized Programs of Research Excellence (SPOREs), and several other lung cancer research programs.

When complete, four reference sets will be available. Two sets will contain retrospectively collected blood samples with clinical annotation, and the other two will contain prospectively collected samples.

The reference sets will be assembled and stored at the NCI facility in Frederick, MD. Any investigator studying promising lung cancer biomarkers can submit an application to the internal LCBG review committee for consideration. The detailed protocol for requesting access to these samples is available at http://edrn.nci.nih.gov/resources/sample-reference-sets.

May is Melanoma Awareness Month

May has been designated as Melanoma/Skin Cancer Awareness Month. An NCI podcast on sun safety and skin cancer is available at http://www.nih.gov/news/radio/index.htm. For information about melanoma risk, prevention, and treatment, go to http://www.cancer.gov/cancertopics/types/melanoma. For information about other types of skin cancer, go to http://www.cancer.gov/cancertopics/types/skin. ◆

Resources for Women's Health Information

- Women's Cancers
- Women and Cancer Survivorship
- NIH Office of Research on Women's Health
- HHS Office on Women's Health
- National Women's Health Information Center
- Other Government Resources for Women's Health

70 YEARS OF EXCELLENCE IN CANCER RESEARCH

If Memory Serves…

The year before the National Cancer Institute Act of 1937, Marjorie G. Illig of the American Society for the Control of Cancer (predecessor of the American Cancer Society) suggested the creation of a legion of female volunteers. The goal of the Women's Field Army was to raise money for cancer research and to educate the public about cancer. Her recruits wore khaki uniforms with insignia for rank and achievement. In less than 3 years, they helped increase the number of volunteers who were active in cancer control by tenfold.

For more information about the birth of NCI, go to http://www.cancer.gov/aboutnci/ncia.

Community Update

Photographer Wins Pulitzer for Cancer Story

This year Renee C. Byer, a senior photojournalist for the *Sacramento Bee*, won a Pulitzer Prize for her photo essay, "A Mother's Journey," capturing the story of single mother Cyndie French and her son Derek Madsen's fatal battle with cancer in 2006. The photos can be viewed at http://www.pulitzer.org/year/2007/feature-photography/works/.

For Byer, this was an important story to tell. "Billions of dollars go to cancer research, but very little is available to help families struggling emotionally and financially throughout this medical crisis. I wanted to bring awareness to that fact and also compassion to other families struggling in the same situation."

Byer first met French while on a photo assignment at the Susan G. Komen Race for the Cure on May 7, 2005. French's 11-year-old son Derek had neuroblastoma, a cancer that arises in immature nerve cells and primarily affects infants and children. French described her emotional and financial hardships and invited Byer to meet her son.

Initially, Byer wasn't sure she could photograph their story. "As a journalist, you have to let scenes unfold, especially in this kind of situation where lifeline decision making is taking place. You don't want to interrupt the family's normal pattern of life or alter their state of mind." She was uncertain whether Derek would let his guard down enough for her to do this, and she was afraid of how emotionally invested she might become in their lives.

"It's a tough balancing act between stepping back and being compassionate as a person. But what this family endured is tenfold what I endured, so that is how I could document their story."

For a year, Byer captured their visits to the doctor, grocery store trips, and moments of joy, anger, and sorrow. Now Byer hopes that the photos and Pulitzer Prize will draw attention to Derek's Wish, a foundation that French has started in memory of her son to assist other families who are going through treatment for terminal cancer.

The Pulitzer Prizes were created by journalist and newspaper magnate Joseph Pulitzer through an endowment to Columbia University. Pulitzer regarded journalism as a noble and important profession for its influence on the "minds and morals of the people."

The awards are now funded through a foundation and are awarded each April by the president of Columbia University for outstanding achievements in journalism, upon the recommendations of a voting board. Submissions total more than 2,400 each year for 21 categories. The winners receive $10,000 at a ceremony in May.

Information about financial resources for cancer patients can be found at http://www.cancer.gov/cancertopics/factsheet/Support/financial-resources. NCI's Office of Cancer Survivorship has additional information for cancer patients and their families. ◆

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_051507/page11. ◆

The *NCI Cancer Bulletin* is produced by the National Cancer Institute (NCI). NCI, which was established in 1937, leads the national effort to eliminate the suffering and death due to cancer. Through basic, clinical, and population-based biomedical research and training, NCI conducts and supports research that will lead to a future in which we can identify the environmental and genetic causes of cancer, prevent cancer before it starts, identify cancers that do develop at the earliest stage, eliminate cancers through innovative treatment interventions, and biologically control those cancers that we cannot eliminate so they become manageable, chronic diseases.

For more information on cancer, call 1-800-4-CANCER or visit http://www.cancer.gov.

NCI Cancer Bulletin staff can be reached at ncicancerbulletin@mail.nih.gov.