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SPORE Study Provides New Guidelines for Tamoxifen Use

Approximately half a million women in the United States alone currently take the drug tamoxifen, either as an adjuvant therapy for preinvasive or invasive breast cancer, or as a chemopreventive agent for those at high risk of the disease.

Now, a new study led by Dr. Matthew Goetz, an investigator for the Breast Cancer Specialized Program of Research Excellence (SPORE) at the Mayo Clinic, has shown that up to 10 percent of women taking the drug may not receive the intended benefit due to genetic differences in the way tamoxifen is metabolized. Additionally, a larger percentage of women may be at increased risk of treatment failure because of drug interactions.

Both genetic polymorphisms and many commonly administered drugs—such as selective serotonin reuptake inhibitors—can affect the activity of an enzyme called cytochrome (CYP) 2D6. Dr. David Flockhart's group, which is funded by the National Institute of General Medical Science's Pharmacogenetics Research Network, has performed

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Director's Update

The Power of Numbers: Melding Genomics and Epidemiology

NCI is moving on a number of fronts to harness the power of new genomic technology through epidemiologic studies designed to uncover gene variants that contribute to cancer susceptibility. Findings from NCI's portfolio of family studies have formed the basis for our understanding of many high-penetrant cancer-causing mutations. These rare mutations give unprecedented insights into carcinogenic mechanisms, but are responsible for only a small proportion of all cancer. Most cancer risk is believed to be due to gene-environment interactions involving low-penetrant but common genetic variants or single nucleotide polymorphisms (SNPs).

As outlined at last week's meeting of the National Cancer Advisory Board, some of the most promising of these studies of susceptibility genes are being led by investigators in NCI's Division of Cancer Epidemiology and Genetics (DCEG). Together with colleagues in the Division of Cancer Control and Population Sciences (DCCPS) and Office of Cancer Genomics, they have joined forces with extramural collaborators to form strategic partnerships that link epidemiologists, genomicists, and other investigators from the clinical, basic, and population sciences. This transdisciplinary team-based approach

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extensive basic science work and early clinical studies demonstrating that CYP2D6 activates tamoxifen, producing a molecule called endoxifen, which is thought to be the metabolite primarily responsible for tamoxifen's therapeutic effect.

"Basic science has told us for the past 30 years that this enzyme is genetically polymorphic, and we expected people with the polymorphisms to make about five times less of the active metabolite," explained Dr. Flockhart, chief of the Division of Clinical Pharmacology at Indiana University and a collaborator on the SPORE project.

The SPORE data used to test this hypothesis came from a prospective randomized trial conducted by the North Central Cancer Treatment Group, in which postmenopausal women were administered 5 years of tamoxifen therapy for estrogen-receptor-positive breast cancer. Both CYP2D6 genotype and medications that interfere with CYP2D6 were known for 180 women randomly assigned to the tamoxifen-only control arm of the trial.

Researchers classified 65 of these women as having decreased metabolism of tamoxifen based on expected genetic or drug-induced inhibition of CYP2D6. The SPORE investigators then compared time to breast cancer recurrence, disease-free survival, and overall survival between those with decreased CYP2D6 metabolism and the 115 patients expected to metabolize tamoxifen normally.

The clinical benefit of tamoxifen was greatly decreased for women with factors that negatively affected CYP2D6 metabolism. These women had significantly shorter time to disease recurrence and significantly worse disease-free survival compared with women able to metabolize the drug normally. Women with the largest decrease in CYP2D6 metabolism (CYP2D6 poor metabolizers or those taking a potent CYP2D6 inhibitor) had a threefold higher risk of breast cancer recurrence while taking tamoxifen. The final results from this study, which was also funded by a K-12 training grant to Dr. Goetz, were published online November 18 in *Breast Cancer Research and Treatment*.

On October 18, a presentation of this study and related historical data by Dr. Goetz to the Food and Drug Administration led to an advisory committee unanimously recommending a label change for tamoxifen. This change would include information about the increased risk both from genetic factors and drug interactions affecting CYP2D6. The majority of the committee also recommended that the label mention CYP2D6 genotype testing as an option for women before they are prescribed tamoxifen.

"The promise of pharmacogenetics is the ability to individualize therapy for our patients," said Dr. Goetz. "In the case of tamoxifen, CYP2D6 may be a marker which identifies patients who can be successfully treated with sequential tamoxifen followed by an aromatase inhibitor or who should be treated up front with an aromatase inhibitor."

However, he explained, prospective clinical trials are needed to identify whether selecting breast cancer patients for tamoxifen therapy based on genetic variability in CYP2D6 will lead to superior clinical outcomes. ◆

By Sharon Reynolds

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responds to a growing consensus in the scientific community that realizing the full potential of genomic and other new technologies requires their integration into robust, large-scale epidemiologic studies.

This can be accomplished through consortia that combine resources of several large cohort and/or case-control studies in a coordinated approach that allows rapid replication of positive findings. One such unique partnership is the Cohort Consortium, an international collaboration of intramural and extramural investigators responsible for 23 population cohorts encompassing 1.2 million individuals. The Cohort Consortium provides an integrative framework for nested case-control studies of specific cancers arising within the cohorts to systematically evaluate molecular and biochemical biomarkers of susceptibility and disease.

DCEG investigators are attempting to identify cancer susceptibility genes using the pathway-driven approach and genome-wide association studies (GWAS). The former approach involves studies that investigate risks associated with candidate genes selected on the basis of known function or biologic plausibility. For example, in a case-control study conducted in Spain and published last year in *Lancet*, DCEG's Dr. Montserrat Garcia-Closas and colleagues at NCI and in Spain showed that SNPs in two candidate genes, *NAT2* and *GSTM1*, were associated with increased risk of bladder cancer and modified the risk due to cigarette smoking. Although the relative risks were modest, these SNPs are common among bladder cancer patients and may contribute to nearly one-third of the cases.

In contrast, GWAS use the latest technologies to "interrogate" the entire genome without targeting any specific gene. Led by a team of

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Cancer Research Highlights

Drug Prevents Mammary Tumors in Mice by Reducing Progesterone Activity

Researchers have found that inhibiting the activity of the hormone progesterone can prevent the development of mammary tumors in mice that carry mutations in a rodent version of the human breast cancer gene *BRCA1*. Mutant mice treated with the drug RU486, the "morning after" pill (also known as mifepristone and Mifeprex), did not develop mammary tumors by the time they were a year old, while the untreated mice developed tumors by 8 months of age.

Women who inherit *BRCA1* gene mutations are at an increased risk of breast and ovarian cancers, and many reduce their risk by having their ovaries or breasts surgically removed. Though the new research was done in mice, the findings raise the possibility that inhibiting progesterone might be an additional strategy for reducing the breast cancer risk among these women.

High progesterone levels have been linked to an increased risk of breast cancer, and this study suggests a mechanism. Dr. Eva Lee of the University of California, Irvine, and her colleagues propose that the normal BRCA1 protein may help protect against breast cancer by helping to degrade the receptor protein that binds to progesterone.

If the progesterone receptor is not broken down, then the hormone's growth-promoting signal persists, and this may lead to excessive cell growth and cancer, the researchers reported in the December 1 *Science*. To reduce the hormone's signal, they tested mifepristone, which inhibits the progesterone receptor, and found that it prevented mammary tumors from developing.

The results suggest that the progesterone receptor function may be critical to the development of breast cancer in the presence of *BRCA1* mutations. "These findings reveal a tissue-specific function for the BRCA1 protein and raise the possibility that antiprogesterone treatment may be useful for cancer prevention in individuals with *BRCA1* mutations," the researchers concluded.

Previous research has suggested that the normal BRCA1 protein suppresses tumors by repairing damaged DNA before tumors develop, and the regulation of the progesterone receptor levels would be another role for the protein.

Dr. Lee noted that mifepristone has effects on other hormones in addition to progesterone and therefore might not be ideal for long-term use in cancer prevention among women with *BRCA1* mutations. Other progesterone-blocking drugs are in development and may be suitable.

Bacteria, Chemo Combination Shows Potency in Mouse Model

A protein produced by a genetically modified bacterium appears to enhance the tumor-killing ability of common chemotherapy drugs that are encased in fatty capsules called liposomes. Because liposome-encapsulated drugs stay in the body longer, they can more selectively target tumors.

In a study published in the November 24 *Science*, researchers from the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University showed that combination therapy involving the bacterium *C. novyi-NT* and Doxil, which is the liposome-encapsulated version of the chemotherapy drug doxorubicin, in a mouse model of colorectal cancer caused a complete disappearance of tumors in all of the mice tested; two-thirds of the mice survived for more than 3 months. Similar results were seen using a liposome-encapsulated version of the chemotherapy drug irinotecan. There was generally no evidence of toxicity from the treatment.

The same research team, from the lab of Dr. Bert Vogelstein and led by Dr. Ian Cheong, had previously shown that *C. novyi-NT* selectively kills tumor cells in regions of tumors that are receiving little oxygen, while sparing those in the more aerobic tumor "rim." The combination of the modified bacteria and Doxil, they found, delivered higher concentrations of the liposome's contents than could be achieved when Doxil was delivered as a single agent.

After seeing the increased efficacy of the combination therapy, the researchers sought to identify how the bacteria helped achieve this effect. They discovered a previously unidentified protein, which they dubbed liposomase, that seemed to be primarily responsible for efficiently disrupting the liposomes' fatty membrane in the tumor and ensuring

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(Highlights continued from page 3)

that a greater amount of drug was delivered to the tumor cells.

"Because virtually any therapeutic agent can be packaged in liposomes and can thereby act as a 'prodrug,'" they wrote, "liposomase offers a number of possibilities for the specific delivery of drugs to tumors."

Brain Scans Show Structural Effects of Chemotherapy

The cognitive impairments demonstrated by breast cancer patients who undergo chemotherapy—symptoms commonly called "chemobrain"—may be related to structural brain changes, according to Japanese researchers in a study published early online November 27 in *Cancer*.

The researchers used high-resolution brain magnetic resonance imaging to look at the distribution of gray and white brain matter regions in women who received chemotherapy after surgery and women who did not receive chemotherapy, with a set of healthy controls for comparison.

Fifty-one women who received chemotherapy were scanned in the first year after surgery, and 73 women were scanned 3 years after their surgery; 55 women who didn't receive chemotherapy were scanned in the first year after surgery, and 59 were scanned 3 years after surgery. The women received Wechsler Memory Scale-Revised testing for cognitive indices including attention, concentration, and visual memory.

The researchers found that in the first year of chemotherapy treatment, women had smaller right-prefrontal brain regions and smaller parahippocampal gyri—regions that are associated with memory—than women who didn't receive chemotherapy, and these changes correlated with decreased cognitive function. Other areas with similar shrinkage, also associated with memory, included the superior and middle-frontal gyri, the cingulated gyrus, and the precuneus.

By contrast, these structural differences were not seen in the group that was analyzed 3 years after surgery and chemotherapy, leading the authors to suggest "that the brain volume change related to adjuvant chemotherapy may well recover over the course of time." They noted that while other studies have shown cognitive effects lasting longer than 3 years, these studies have also demonstrated eventual cognitive recovery.

Smoking Cessation Web Sites' Usage and Quality Studied

The types of smokers who are accessing the Web and the quality of Web-assisted tobacco intervention (WATI) sites were reported in two studies published in the December 1 *Nicotine & Tobacco Research*. Each study focused on a product developed or study funded by NCI's Tobacco Control Research Branch (TCRB) in DCCPS.

To help developers of smoking cessation programs improve the content and delivery of resources to both groups, the first study compared smokers who use the Internet with those who do not. Using data from the 2003 NCI Health Information National Trends Survey (HINTS), TCRB scientists compared characteristics of 728 Internet-using smokers with 516 non-Internet-using smokers.

"Our results showed that compared with smokers not on the Internet, those on the Internet had higher income and were more likely to be employed, despite having a younger age," noted NCI researchers Drs. Jacqueline L. Stoddard and Erik M. Augustson. "Internet-connected smokers also reported less psychological distress, fewer barriers to health care, and a greater interest in quitting smoking."

For smokers who didn't use the Web, the most common reason cited was a lack of familiarity with the Internet and a concern about the complexity of gaining access. Because this group also reported a high level of trust in information and advice from family and friends, the researchers suggested that campaigns target friends and families of smokers to increase Internet utilization for the purpose of quitting smoking.

A second study surveyed current and former smokers who had visited a WATI site to determine which of the Internet smoking cessation sites were most popular and how smokers rated their quality. The 706 U.S. respondents cited 133 different Web sites. "Surprisingly, two of the three most frequently visited Web sites were owned by tobacco companies," noted researcher Dr. Jean-Francois Etter of the University of Geneva, Switzerland. However, these two sites were not perceived as helpful by smokers, the study reported. In contrast, Smokefree.gov, a U.S. Department of Health and Human Services (HHS) Web site, received the highest quality rating of the sites and was the second most frequently recommended site by smokers to their friends. ◆

NCI 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_120506/page5 ◆

Spotlight

Cancer Prevention Stakes Are High for Dietary Intervention Research

The field of prevention is public health's first line of defense against cancer. A key strategy has become short-term clinical nutrition trials linked to rigorous basic nutritional science, says Dr. Peter Greenwald, director of NCI's Division of Cancer Prevention (DCP).

The presence or absence of certain bioactive food components—along with other lifestyle factors such as exercising throughout life—are now thought to significantly affect one's risk for cancer. Identifying these lifestyle factors "has been one of the most important medical contributions for improving the public health in the past half century," says Dr. Greenwald.

In 1981, the idea became concrete after Drs. Richard Doll and Richard Peto from Oxford University used meta-analysis and epidemiologic studies to show that 30 percent of deaths worldwide were attributable to tobacco. Dietary risk factors were roughly estimated to account for even more—as much as 35 percent of cancer deaths. "However," explains Dr. Greenwald, "although obesity is known to increase risk and physical activity to be beneficial, much more basic nutritional research is needed to better understand the role of bioactive food components."

The epidemiologic lens on nutrition confirms the impact of lifestyle. A recent study led by Dr. Eugenia Calle of the American Cancer Society estimated that "the proportion of all deaths from cancer that is attributable to overweight and obesity in U.S. adults 50 years of age or older may be as high as 14 percent in men and 20 percent in women."

The challenge for cancer prevention is to transform the insights from nutritional science and risk numbers from observational epidemiology into cancers averted and lives saved. Producing scientific evidence is only the first step, notes Dr. Greenwald, because cancer prevention requires changing human behavior in a fundamental way. "Working with city planners, school systems, employers, markets, restaurants, and others in our communities would make this much easier for many people," he explains.

A magic molecule in a pill?

As a society, observes Dr. Greenwald, "We are far more inclined to prescribe than proscribe." Scientists are forever "seeking out simplicity in scientific thinking—in modern times preferably a magic molecule in a pill." Reductionism is a powerful approach to science, but the complex interactions involved in nutrition need the addition of a systems approach.

Multivitamins and mineral supplements (MVMs) are being used by half of American adults, but may produce different effects than the same ingredients that occur naturally in foods. Adverse effects have been linked to megadoses of these ingredients, although most commonly consumed MVMs don't exceed the U.S. Department of Agriculture's Recommended Dietary Allowance (RDA).

In May, NCI and the NIH Office of Dietary Supplements (ODS) were two of the sponsors of the "NIH State-of-the-Science Conference on Multivitamin/Mineral Supplements and Chronic Disease Prevention," which looked closely at the randomized controlled trials evidence. The expert panel concluded that, although dietary supplements and MVMs "are now used by more than half the population…the present evidence is insufficient to recommend either for or against [their use] by the American public to prevent chronic disease."

"It is also important to remember," points out Dr. Paul M. Coates, director of ODS, "that people who take MVMs tend to be more health conscious than nonusers. For example, they're more likely to eat healthier diets and exercise regularly, which makes it harder to determine if the MVMs themselves are actually responsible for any improvements in health."

Back to the drawing board?

Large-scale randomized controlled trials can also swing the other way, not only failing to confirm protective effects from observational epidemiology, but also uncovering harmful effects. "Everyone was surprised when the Alpha-Tocopherol, Beta-Carotene (ATBC) Study and the Beta-Carotene and Retinol Efficacy Trial (CARET) found that beta-carotene supplementation actually increased lung cancer risk in heavy smokers," says Dr. Greenwald.

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ATBC and CARET were 2 of the 9 large phase III trials that composed the first generation of nutritional interventions in cancer prevention, which together enrolled nearly 150,000 participants.

Lessons learned from these first-generation trials will help to evolve the model, notes Dr. Greenwald, because "there are already more exciting leads of how bioactive food components may reduce cancer risk than there are practical possibilities for phase III trials." Thus, newer trials need to reflect what has been learned so far.

The NCI-sponsored 30,000-participant General Nutrition Trial in China tested a number of different pill formulation and packaging complexities, using a design that allows researchers to look at biological interactions between agents and incorporates multiple primary endpoints, assessing other major conditions such as diabetes and cardiovascular disease. Such multifactorial approaches should become a design of choice, Dr. Greenwald and others believe.

A second promising strategy is the use of biomarkers, which could help to establish eligibility criteria for participants and may be a good way to validate how much of the substances being tested actually arrive in the target tissues.

Other technical issues also are critical for more efficient and productive nutrition trials. Certain interventions take longer to manifest their effects; the duration of the intervention should not be set but instead depend on a number of factors.

"It will be important to carefully consider the doses of each dietary supplement ingredient given to study

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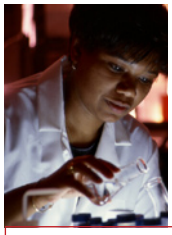


Featured Clinical Trial

Combination Therapy for High-Risk Prostate Cancer

Name of the Trial
Phase III Randomized Study of Androgen Suppression (AS) and Radiotherapy (RT) versus AS and RT followed by Docetaxel and Prednisone in Patients with Localized, High-Risk Prostate Cancer (RTOG-0521). See the protocol summary at http://cancer.gov/clinicaltrials/RTOG-0521.

Principal Investigators
Drs. Howard Sandler, Seth Rosenthal, Oliver Sartor, and Leonard Gomella, Radiation Therapy Oncology Group; Dr. Mark Garzotto, Southwest Oncology Group

Dr. Howard Sandler

Why This Trial Is Important
Although prostate cancer usually grows slowly, it remains the second leading cause of cancer death among American men. When the disease has not yet spread (metastasized) to nearby lymph nodes, patients are diagnosed with localized prostate cancer, but some individuals face a greater risk of disease progression than others, based on higher levels of prostate-specific antigen (PSA) and other clinical signs (higher Gleason score).

No chemotherapy drug has been approved to treat newly diagnosed high-risk patients, who often get radiation therapy to kill cancer cells in and near the prostate, as well as hormone (antiandrogen) therapy to block the growth and spread of cancer cells that survive radiation.

In this trial, after initial radiation and hormone therapy, men with localized, high-risk, androgen-responsive prostate cancer will be treated with the drugs docetaxel and prednisone. Use of these drugs has improved survival—and was approved by the FDA—for patients with metastatic prostate cancer that is no longer responsive to androgens (androgen-independent disease).

"We hope docetaxel's ability to disrupt microtubule biology will prove effective against micrometastatic prostate disease," said Dr. Sandler. Microtubules are an important part of the machinery cells use to divide and multiply. "The other three major cancers—breast, colon, and lung—all respond to adjuvant chemotherapy, and such a treatment would be widely used by prostate patients."

Who Can Join This Trial
Researchers will enroll 600 men aged 18 and over with prostate cancer determined to be at high-risk for recurrence. See the list of eligibility criteria at http://cancer.gov/clinicaltrials/RTOG-0521.

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://cancer.gov/clinicaltrials/RTOG-0521, or call the NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) for more information. The toll-free call is confidential. ◆

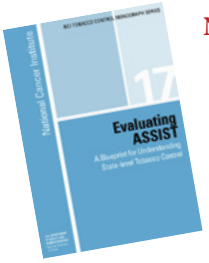
An archive of "Featured Clinical Trial" columns is available at http://cancer.gov/clinicaltrials/ft-all-featured-trials.

Notes

CCR Staff Members Receive NIH World AIDS Day Award

Drs. Robert Yarchoan and Hiroaki (Mitch) Mitsuya of NCI's HIV and Aids Malignancy Branch in the Center for Cancer Research (CCR) will receive the first NIH World AIDS Day Award in recognition for their outstanding scientific contributions to HIV/AIDS research at NIH.

The announcement was made on December 1 to coincide with World AIDS Day. The award, sponsored by the NIH Office of AIDS Research and the National Institute of Allergy and Infectious Diseases, will be presented at a ceremony on January 11, 2007, at the NIH Institute and Center Directors meeting, where the recipients will also give a brief presentation on their research.



NCI Releases New Tobacco Control Monograph

NCI has released the 17th volume in the Tobacco Control Monograph series, *Evaluating ASSIST: A Blueprint for Understanding State-Level Tobacco Control*, which evaluates the American Stop Smoking Intervention Study for Cancer Prevention (ASSIST), one of the largest publicly funded tobacco-use prevention and control efforts in history.

Intended for health professionals, the monograph explains the conceptual framework and methodological approach used in the evaluation, a paradigm that will be useful in assessing future tobacco-use prevention and control efforts in the United States and around the world.

As one measure of its success, ASSIST interventions were adopted in numerous settings beyond ASSIST states, and tailored to state and local conditions. Aspects of the intervention strategy are now being applied to other public health issues, such as physical inactivity and obesity.

The monograph can be found at http://cancercontrol.cancer.gov/tcrb/monographs/17/index.html. Print copies also are available free of charge.

NCI Introduces New Database

The Pathway Interaction Database, a collaborative project between NCI and the Nature Publishing Group, is a new resource aimed at providing insight into biological challenges by exploiting biomolecular interaction data. The database contains fully curated, network-level representations of interactions and pathways. A Web query interface supports simple browsing across predefined pathways, construction of larger networks around molecules and predefined pathways of interest, and analysis and visualization of lists of targeted molecules in the context of predefined and novel networks.

The "NCI-Nature Curated" section of the database currently contains 32 pathways and 1,327 interactions. Each of these pathways is verified by one or more experts in the field. All pathways and interactions are human.

CCR to Sponsor Cancer Prevention Think Tank

NCI's CCR is sponsoring "Cancer Prevention Think Tank 2006" on December 8 at NCI-Frederick.

The forum aims to identify and prioritize promising opportunities for high-impact cancer prevention research, and to enhance a collaborative response to these opportunities within CCR and with other NCI divisions, including the Division of Cancer Treatment and Diagnosis and DCP. NCI and non-NCI speakers, plus two panels of experts, will address the following questions during a full-day's agenda: What are the best molecular targets for cancer prevention? Are there biomarkers that reliably predict the likelihood of cancer endpoints? Can molecularly targeted nutritional interventions be designed? What prevention studies should get high priority?

For more information, go to http://web.ncifcrf.gov/events/CancerPreventionThinkTank2006/default.asp.

Geographical Information Systems Inform Cancer Research

A new brochure from DCCPS, *Geographical Information Systems (GIS) and Cancer Research*, provides an introduction to GIS for cancer researchers who do not currently use the technology in their work.

The brochure includes information on how to use GIS in cancer research, applications for specific areas of research, resources available, research and funding opportunities, and examples of landmark studies.

NCI can help researchers use GIS by providing tools to analyze spatial patterns and trends, and to evaluate the impact of cancer control interventions, as well as geographic, social, behavioral, genetic, and health care delivery factors on the cancer burden.

For more information on GIS, go to http://gis.cancer.gov. To order a copy of the brochure, go to https://cissecure.nci.nih.gov/ncipubs/search.asp. ◆

(Director's Update continued from page 2)
DCEG and extramural epidemiologists, statisticians, and genomicists, the Cancer Genetic Markers of Susceptibility (CGEMS) project is using high-throughput technology to identify and validate susceptibility genes for breast and prostate cancer. The potential associations identified will be validated in subsequent studies to eliminate false-positives due to chance. To date, GWAS have been completed on 1,200 prostate cancer cases and controls, and the data have been made available on NCI's cancer Biomedical Informatics Grid™ (caBIG™). It is anticipated that the initial scan for breast cancer will be posted in early 2007, and plans are underway to launch a similar scan for pancreatic cancer.

We believe that these highly collaborative strategies currently will provide the scientific community with unprecedented opportunities to understand cancer susceptibility mechanisms, including gene-environment interactions, and thus inform new strategies to accelerate the prevention, early detection, and treatment of cancer. ◆

Dr. John E. Niederhuber
Director, National Cancer Institute

NCI Cancer Bulletin Publication Break

Next week's special issue on the 35th anniversary of the National Cancer Act, which Cancer.gov currently commemorates, will be our final issue of 2006.

Since today's edition is the last regular issue of the year, the editors and writers of the *NCI Cancer Bulletin* would like to wish all of our readers a happy and healthy holiday season. We will resume publication on our usual schedule with the January 2, 2007, issue. ◆

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participants," says Dr. Coates. "Rather than megadoses, they should be in line with RDA levels."

"The beta-carotene/lung cancer link established a new paradigm for how to think about potential side effects," says Dr. Greenwald, which requires careful consideration beyond effects on cancer alone to monitor other major causes of morbidity and mortality.

Careful thinking about how to prepare for and mount such trials was a primary goal of a 2003 workshop at the Fred Hutchison Cancer Center entitled "Research Strategies for the Study of Nutrition, Physical Activity and Chronic Disease."

"We came away with a very cogent, though admittedly ambitious, set of recommendations," says Dr. John Milner, chief of DCP's Nutritional Sciences Research Group. "When an intervention appears biologically plausible and promises substantial potential benefits for the public health, funding should be found to mount a full-scale clinical trial."

Dr. Greenwald sees a bright future for nutritional intervention research. He believes short-term phase II trials linked to intensive basic nutrition science studies are a key direction for the future. These will include use of modern research technologies. When enough evidence has been gathered to make the case for a large-scale trial, these generally should have multiple disease endpoints, biorepositories, and long-term follow-up of the participants to document late beneficial or adverse effects. ◆

By Addison Greenwood

NCI Listens and Learns

The cancer Biomedical Informatics Grid™ (caBIG™) is a voluntary cancer research network of infrastructure, tools, and ideas that enables individuals and institutions to share data to speed the delivery of innovative approaches for cancer prevention and treatment. NCI would like feedback from the advocacy community and the public about caBIG™.

- NCI has created a caBIG™ Web site specifically for public use at http://cabig.cancer.gov/. What ways might the site be strengthened to educate the patient advocacy community about the caBIG™ initiative?
- What benefits or concerns do cancer patients and advocacy organizations see related to the caBIG™ initiative?

To register and post comments, go to http://ncilistens.cancer.gov. ◆

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.