NATIONAL CANCER INSTITUTE

NCI Cancer Bulletin

A Trusted Source for Cancer Research News

February 5, 2008
Volume 5 | Number 3

In this issue:

A Publication of the
National Cancer Institute
U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
National Institutes of Health
NIH Publication No. 05-5498
http://www.cancer.gov

Oral Contraceptives Reduce Long-Term Risk of Ovarian Cancer

Since they were first licensed nearly 50 years ago, birth control pills containing estrogen have prevented some 200,000 cases of ovarian cancer world-wide, estimate the authors of a study published January 26 in *The Lancet.* Further, in the absence of having taken oral contraceptives, half of these women would have died of the disease.

The researchers showed that oral contraceptives (OCs) continue to confer protection for years—even decades—after women stop using them. Thus, they surmise, "the number of ovarian cancers prevented [will] rise over the next few decades" to at least 30,000 each year.

These figures emerge from a comprehensive meta-analysis based on prospective and case-control data from 45 epidemiological studies in 21 countries, mostly in Europe and the United States. "These findings set a new standard in prevention for a deadly cancer," wrote the editors of *The Lancet*, "and have important public health implications."

The results showed that women who had ever taken OCs were 27 percent less likely to develop ovarian cancer. The studies included 23,257 women with ovarian cancer, 31 percent of whom had taken OCs; of the 87,303 controls, 37 percent took OCs.

Two trends emerged that were really striking, according to Dr. Beth Karlan, editor-in-chief of *Gynecologic Oncology* and director of the Gilda Radner Cancer Detection Program at Cedars-Sinai Outpatient Cancer Center in Los Angeles. First, the longer OCs were used, the greater the ovarian cancer risk reduction, decreasing about 20 percent for

(continued on page 3)

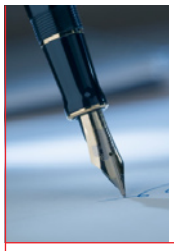
Cancer Research Highlights

Sorafenib Increases Risk of High Blood Pressure

A meta-analysis published online January 24 in *Lancet Oncology* reports that patients receiving the standard clinical dose of sorafenib (Nexavar), an anticancer drug that targets the growth of tumor blood vessels, or angiogenesis, have a significantly increased incidence of hypertension.

Previous studies have found an increased risk of hypertension with the use of other targeted drugs and antiangiogenesis agents, including sunitinib (Sutent). To see if sorafenib also increases this risk, and subsequent risk of heart attacks and other serious cardiac events, the authors combined clinical trials data from three published papers and six meet-

(continued on page 4)



Director's Update

Budget Proposal Highlights Cancer Research Progress, Priorities

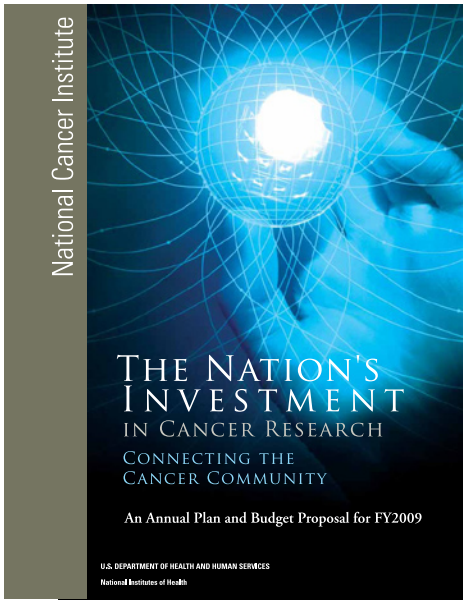
Among the most valuable communication tools created as a result of the National Cancer Act of 1971 is the NCI's annual report on *The Nation's Investment in Cancer Research*, which was released this week. Often referred to as the "bypass budget," this report is intended to directly inform the President and guide the administration's budget request to Congress for NCI funding.

It was designed by its originators, led by Rep. Paul Rogers, to lay out in detail for the President what is needed to make as rapid progress as possible to change the course of this disease, and to provide NCI with the resources required to lead the National Cancer Program.

The Nation's Investment tells the story of scientific opportunity, emphasizing critical areas of progress in cancer research and highlighting key NCI programs that will drive future gains. It also offers insight into NCI's scientific planning and priorities, including what is called the "professional judgment budget."

This budget contains two different proposals: the budget NCI leadership believes is needed to simply sustain the National Cancer Program in its current state, and the budget required to launch new and expand current initiatives that NCI feels can hasten progress.

For fiscal year (FY) 2009, NCI's proposed budget to simply sustain our current level of activities is approximately $5.2 billion, while the proposal to accelerate progress is approximately $6 billion. By comparison, NCI's FY 2007 budget was approximately $4.8 billion.



Any report of this kind being delivered in 2008 cannot escape some difficult facts, namely that we have been operating under a flat budget for the last 4 years. And because of the continued brisk pace of biomedical inflation, the chief result has been a 12 percent reduction in NCI's purchasing power over that same period.

This lost purchasing power has had serious consequences. They include extramural laboratories cutting back on postdoctoral fellows, fewer resources with which to conduct needed clinical trials and fewer patients in already funded trials, and scaling back important programs and foregoing the launch of new programs, to cite just a few examples. And one particularly concerning repercussion of such problems is the serious impact on promising young investigators, many of whom have been choosing alternate career paths.

While progress will continue in all important areas of cancer research, it is clear that the pace of our progress is closely aligned with our available resources and, therefore, will be significantly slowed.

The Nation's Investment in Cancer Research illustrates how NCI is using its resources to support the best science and ensure continued advances, with an acute focus on how we are establishing the necessary infrastructure and programs to more closely connect important components of the cancer and larger biomedical research communities.

These areas include critical initiatives like the Glioma Molecular Diagnostics Initiative, a collaborative effort spearheaded by NCI's Dr. Howard Fine. The GMDI is bringing together NCI cancer centers and cooperative groups, the pharmaceutical industry, brain tumor consortia, and other NIH institutes to develop more individualized therapies for gliomas, particularly glioblastomas, a highly aggressive and often fatal type of brain cancer.

We are creating new connections through the National Community Cancer Centers Program, which will bring clinical trials closer to patients in their communities and allow us to conduct important research on quality of and disparities in care.

We are recruiting researchers from different disciplines to jointly tackle

(continued on page 3)

(Director's Update continued from page 2)

the most urgent problems in collaborative research networks. For example, the Tumor Microenvironment Network is enlisting cancer biologists, pathologists, and bioinformatics specialists, among others, to delve further into what we now understand is the critical role a tumor's immediate environment plays in its development and metastatic potential.

Through the Chemoprevention Research Consortium, we are translating promising lab results of new chemoprevention agents into phase I and II human clinical trials, setting the stage for the phase III trials that can determine the most effective and safest chemoprevention drugs for patients at increased cancer risk.

We are connecting the past and future through NCI's rapidly evolving training programs to help produce the next generation of cancer researchers, and via NCI's Spanish-language Web site, we are reaching out to native Spanish speakers with vital information on cancer and cancer research.

Information on all of this and much more is in this year's report, and I encourage the cancer community to take advantage of it and other NCI communications tools, both for your own information and to inform your own research or outreach efforts. ◆

Dr. John E. Niederhuber
Director, National Cancer Institute

(Oral Contraceptives continued from page 1)

each 5 years of use.

The second clear trend was the duration of the protective effects, which lasted long after women had stopped using OCs. For each 5 years of use, risk of developing ovarian cancer was reduced 29 percent in the first 10 years after stopping. The risk reduction was still significant though smaller (19 percent) for years 10–20, and smaller still (15 percent) 20–29 years after discontinuation.

Another feature of these results is their uniformity. OCs seem to protect against nearly all types of epithelial and nonepithelial tumors, with the possible exception of mucinous ovarian cancer (which accounted for only 12 percent of cases studied in the meta-analysis). *The Lancet* editorial points out that the results show "the benefits of oral contraceptives are independent of the preparation [estrogen dose], and vary little by ethnic origin, parity, family history of breast cancer, body-mass index, and use of hormone replacement therapy."

Representatives from nearly all of these studies—including Drs. Patricia Hartge, James Lacey, Louise Brinton, and Robert Hoover from the Epidemiology and Biostatistics Program in NCI's Division of Cancer Epidemiology and Genetics (DCEG)—worked together to ensure the integrity of the analysis, forming the Collaborative Group on Epidemiological Studies of Ovarian Cancer, under the leadership of Dr. Valerie Beral and colleagues at Oxford University's Cancer Research UK Epidemiology Unit.

The absence of proven screening methods for ovarian cancer make these findings all the more welcome. But the issue is not straightforward, because calculating "the net effect on women's health is fraught with uncertainties," wrote Drs. Eduardo L. Franco and Eliane Duarte-Franco of McGill University in Montreal in a comment accompanying the article. They went on to list possible side effects of OCs as increased risk of thromboembolism, heart disease, migraine, liver disease, and several other relatively uncommon conditions.

The analyses were not focused on comparing the benefits and risks of OCs, explains DCEG's Dr. Brinton, but only examined their effect on ovarian cancer risk. In the absence of detailed risk-benefit data, including currently unknown risks, such as cancers in women who have taken OCs and later take long-term hormone replacement therapy, she says, "This meta-analysis does not recommend widespread prescription of OCs as a preventative measure against ovarian cancer."

Dr. Beral commented that while OCs may pose a slight increased risk of breast and cervical cancer, the effect is small and disappears once the drugs are no longer being used, as contrasted with the ongoing protective effect against ovarian cancer.

Dr. Karlan added, "Ovarian cancer remains a disease with a high mortality due [mainly] to our inability to reliably diagnose it at an early stage. Women are concerned about this risk." She noted that it is important for women to be aware that OCs reduce that risk when discussing their contraceptive choices with their health care providers. ◆

By Addison Greenwood

Cancer Research Highlights

(continued from page 1)

ing abstracts that included data on hypertension for patients assigned a starting dose of 400 mg of sorafenib twice daily, which is the current starting dosage approved by the FDA.

From these 9 studies, 4,599 patients were available for analysis; 3,567 received sorafenib and the other 1,032 served as controls. Data on all grades of hypertension were available from 3,363 patients enrolled in 7 trials. The overall incidence of all-grade hypertension was 23.4 percent in patients receiving sorafenib. Patients taking sorafenib were approximately six times as likely to develop any grade of hypertension as the control patients.

Data on high-grade hypertension, which often requires treatment with multiple antihypertensive drugs or discontinuation of sorafenib, were available from all 3,567 patients in the 9 trials who received the drug. The overall incidence of high-grade hypertension was 5.7 percent for these patients.

"The hypertensive and cardiovascular side-effects of sorafenib need thorough postmarketing surveillance and reporting, and future studies will be needed to identify the mechanism and appropriate treatment of sorafenib-induced hypertension," conclude the authors. In particular, they explain, further studies need to identify the classes of antihypertensive medications that can be safely given in tandem with sorafenib to minimize potential drug-drug interactions and possible interference with the efficacy of sorafenib.

Clinical Outcomes in Colon Cancer Linked to microRNA Gene

Colon tumors that produced high expression levels of a microRNA gene called *miR-21* were associated with poor survival and therapeutic outcome in two patient populations, one in the U.S. and the other in China, according to a study in the January 30 *Journal of the American Medical Association*.

Like other microRNA genes, *miR-21* produces short strands of RNA that control multiple genes, including some involved in cancer. The findings support a growing view that this gene, which shows increased activity in more than a dozen major cancers, may be a useful biological marker and therapeutic target.

"We are interested in this gene in part because our results may have implications for other cancers," said Dr. Curtis Harris of NCI's Center for Cancer Research (CCR), who led the study. "And a therapy directed against *miR-21* may be effective against a variety of cancers." He cautioned that the results are preliminary and potential therapies may be years away.

The researchers first profiled microRNA gene activity in colon tumors and matched normal tissues from 84 patients from Maryland, and they validated the results in 113 patients from Hong Kong. The most striking finding was the association between high *miR-21* activity in tumors and poor survival and therapeutic outcome in patients receiving adjuvant chemotherapy based on 5-fluorouracil. The associations were consistent even though slightly different techniques were used to assess microRNA activity in each group.

The results also indicate that microRNA gene activity is systematically altered in colon tumors compared to normal tissues. "There are systematic changes in microRNA expression during the cancer process," said first author Dr. Aaron Schetter of NCI's CCR.

Protein in Breast Tumors Does Not Predict Chemotherapy Benefit

High levels of the protein Ki-67 in breast tumors did not predict which women in two clinical trials would benefit from chemotherapy added to endocrine (antiestrogen) therapy. Some studies have suggested that the protein, which is associated with cell proliferation, might be used to identify women with early-stage disease who may benefit from adjuvant chemotherapy after surgery and endocrine therapy.

To test this idea, Dr. Giuseppe Viale of the University of Milan and his colleagues in the International Breast Cancer Study Group retrospectively assessed Ki-67 expression in tumors from patients involved in two randomized trials—each of which compared endocrine therapy given after chemotherapy with endocrine therapy alone. The analysis included only women with early-stage, lymph node-negative disease.

Although high levels of Ki-67 expression did not predict a chemotherapy benefit, they were prognostic of poor survival. "Other biomarkers will be required to define which patients with endocrine-responsive, node-negative early breast cancer would

(continued on page 5)

(Highlights continued from page 4)

benefit from the addition of adjuvant chemotherapy to endocrine therapy," the researchers conclude in the February 6 *Journal of the National Cancer Institute (JNCI)*.

The study supports the long-held position of the American Society of Clinical Oncology Tumor Marker Expert Panel that measurements of the cell cycle, such as Ki-67 expression, should not be used to make decisions about chemotherapy.

In an accompanying editorial, Dr. Matthew Ellis of Washington University in St. Louis says that biomarker studies with negative results that can exclude a positive interaction are important to publish because "clinging to a long-favored but incorrect hypothesis in the face of negative evidence impedes scientific and clinical progress."

Survey Highlights Threat of Global Tobacco-Related Mortality

Results of a new World Health Organization (WHO)-led survey of youths ages 13 to 15 suggest that the already alarmingly high number of tobacco-related deaths estimated to occur annually by 2020 may be too low, officials from the Centers for Disease Control and Prevention (CDC) and colleagues report.

By 2020, global tobacco-related deaths are estimated to double from 5 million a year to 10 million. Approximately 70 percent of these deaths will occur in developing countries.

But the results of the most recent Global Youth Tobacco Survey (GYTS)—an international, school-based survey conducted in 140 WHO member nations and other sites—suggest the situation may be worse than previously thought, wrote Dr. Charles W. Warren and colleagues in the January 25 *Morbidity and Mortality Weekly Report*.

Among the findings are a higher prevalence of young female smokers compared with adult females, the "high susceptibility" to smoking in the next year reported by never-smokers, and elevated levels of exposure to secondhand smoke.

Other key findings included the similar prevalence of cigarette and other tobacco product use and the high percentage of respondents who had recently bought tobacco products at a store without being refused service. Seventy percent of respondents who smoke expressed an interest in quitting, while 80 percent of all respondents supported a public ban on smoking.

"The findings in this report suggest that interventions that decrease tobacco use among youth (e.g., increasing excise taxes, media campaigns, school programs in conjunction with community interventions, and community interventions that decrease minors' access to tobacco) must be broad-based, focused on boys and girls, and have components directed toward prevention and cessation," the authors wrote.

Expanding the Search for Cancer Drug Targets

Two studies in the February 1 *Science* describe a genome-wide strategy for discovering "essential" genes in cancer cells that are toxic to the cells when silenced. These genes may lack the hallmarks of cancer genes, such as mutations or increased activity; however, they are essential for cell survival and proliferation, making them potential drug targets.

The strategy, described in the first study, exploits a natural defense mechanism in cells that blocks invading viruses by degrading viral RNA. Researchers now use this mechanism, known as RNA interference, as a way to target and silence genes within the cell. But technical constraints have prevented researchers from doing this type of screen on a genome-wide scale.

During the last 6 years, Drs. Stephen J. Elledge of Harvard Medical School, Gregory Hannon of Cold Spring Harbor Laboratory, and their colleagues have been working to change that. Among other advances, the researchers developed libraries of short hairpin RNA molecules that can silence every gene in the human and mouse genomes. They also created a system for using molecular tags, or bar codes, to determine which genes were toxic to cancer cells when deleted from the cells.

As reported in the second study in *Science*, the researchers screened several thousand genes in colon and breast tumor cells, as well as in normal cells—using some 10,000 short hairpin RNAs. They identified a few dozen genes that, when silenced, impaired the growth of cancer cells but not normal cells. The researchers believe the results are preliminary but promising.

The strategy could complement The Cancer Genome Atlas and other large-scale efforts to catalog genetic differences between tumor cells and normal cells, they continued. Specifically, the screens could reveal potential therapeutic targets that might otherwise be missed.

"I've always felt that the focus on oncogene addiction in developing cancer drugs was missing a lot of other cancer drug targets," says

(continued on page 6)

(Highlights continued from page 5)

Dr. Elledge, referring to the phenomenon where tumors become dependent on certain cancer-causing genes. "Cancer cells seem to depend on a lot of genes that are not oncogenes, but they are important nonetheless. We call this non-oncogene addiction."

His team is preparing to apply the strategy against the entire human genome. At the same time, they hope other researchers will begin to apply the tools and the methods to many different types of cancers. Now that the resources have been developed, carrying out the experiments is relatively cost effective, the researchers note.

Study Finds No Link Between Hormones, Prostate Cancer

An analysis of the original data from 18 prospective studies indicates that prostate cancer risk is not influenced by levels of certain circulating sex hormones in the blood, reports an international research team.

Published early online January 29 in *JNCI*, the analysis pooled data from studies that included 3,886 men with prostate cancer and 6,438 controls. Contrary to what has long been suspected but never definitively established, no association was found between prostate cancer risk—regardless of stage or grade—and levels of various androgens as well as estradiol, a form of estrogen.

Further, reported Dr. Andrew Roddam of the University of Oxford and colleagues from the Endogenous Hormones and Prostate Cancer Collaborative Group, "there was no evidence of interactions between concentrations of any of the hormones considered and risk of prostate cancer." There was, however, a slight reduction in the risk of low-grade, localized cancer associated with circulating levels of sex hormone-binding globulins (SHBGs).

"The factors that promote localized or nonaggressive prostate cancer may be entirely different than those that promote fast-growing, high-grade prostate cancers," wrote Dr. Paul Godley and colleagues from the University of North Carolina at Chapel Hill, in an accompanying editorial. "Because most of the cancers included in these studies were localized and low-grade, pooling data from many studies allowed a sample size that was large enough to perform subanalyses of advanced and high-grade cancers, and the power to investigate interactions among hormones and [SHBGs]."

The study results suggest that "perhaps it is time for research efforts to focus instead on developing more sophisticated hypotheses and novel study designs," the editorial concluded, which can be facilitated by NIH and NCI programs already in place, including the NIH Roadmap and biospecimen storage systems. ◆

Notes

NCAB Hears Update on NCI Budget

At the National Cancer Advisory Board's (NCAB) February 5 meeting, NCI Director Dr. John Niederhuber briefed committee members on a variety of issues, including the Institute's operating budget for fiscal year (FY) 2008. The $4.8 billion appropriation is essentially flat compared with FY 2007, requiring NCI leaders to initiate 3-percent reductions across each NCI division, office, and center. This will include reducing: competing research project grants from 1,312 to 1,283; patient accruals for Community Clinical Oncology Program (CCOP) trials; and funding for long-term cancer survivorship research by $1.7 million. He also stressed the importance of NCI's Bypass Budget report as the leadership's "professional judgment" for what could be accomplished with NCI's current capabilities.

Another highlight during the morning session was a presentation by NIH Director Dr. Elias Zerhouni. He shared data on the aging of NIH-funded investigators. This accelerating trend threatens to "de-prime the pump" in the coming years for developing new investigators who are able to get first-time grants and renewal grants, said Dr. Zerhouni.

The NCAB meeting will conclude tomorrow afternoon. A full copy of the meeting agenda can be found at http://deainfo.nci.nih.gov/advisory/ncab/145_0208/agenda.pdf. A videocast of the 2-day meeting can be found later this week at http://videocast.nih.gov/PastEvents.asp.

EDRN Report Released

The fourth report from NCI's Early Detection Research Network (EDRN), *Investing in Translational Research on Biomarkers of Early Cancer and Cancer Risk,* was released last week. The report is available at http://prevention.cancer.gov/files/edrn4th.pdf. Information about EDRN is available at http://edrn.nci.nih.gov/. ◆

Spotlight

Women with Breast Cancer Talk about Pain

"Make sure people are aware of what I found out, that you don't have to be in pain." —Breast cancer survivor, Toronto

Reader suggested

Pain remains a major problem for people with cancer. Despite recent advances in understanding and managing pain, the majority of cancer patients experience pain that goes untreated or undertreated. A number of factors may help explain this, with the health care system, clinicians, and patients all playing a role.

Busy physicians and nurses may lack incentives to spend time talking with patients about managing pain, for instance, while government regulations limit the use of certain pain medications. Many health care professionals themselves are not adequately trained in managing pain effectively.

Many patients, for their part, are reluctant to mention pain. Some may not want to distract physicians from treating the cancer, or they may view talking about pain as complaining—as not being a "good" patient.

Most important, many assume that pain and cancer go hand-in-hand—that pain is inevitable, something to "tough out." In fact, cancer pain can be effectively controlled in most cases, and experts have been fighting these misconceptions for years.

Such beliefs were common among 18 Canadian women with breast cancer who were recently interviewed about their experiences with pain. A summary of the interviews, published in the February *Journal of Pain and Symptom Management*, provides a comprehensive look at questions about pain from a group of cancer patients.

The interviews also offer a window on experiences that were, in some cases, made more difficult because the women did not know how to get help for their pain. Unfortunately, this is not uncommon among cancer patients, says Jackie Bender, a doctoral student at the University of Toronto and the study's first author.

Her interviews consistently showed that patients lacked knowledge about the options for controlling pain, the services available for managing pain, and how to access them. She was struck that patients did not initially know such services existed.

As one woman said, "Why should I know that there are pain doctors or pain specialists out there? I had no idea."

"Many of the women I spoke to experienced severe pain that had not been managed well," says Ms. Bender. "Fortunately, when I spoke to them, they were receiving help from pain specialists." At the time of the interviews the majority—more than 70 percent—were experiencing mild pain.

One woman commented, "I wish I knew then that there was a painkiller like this to alleviate my pain because …then, I wouldn't have suffered so much, right?"

The descriptions of pain were sometimes accompanied by concerns about addiction and tolerance, particularly with respect to opioid drugs. Such concerns are common among cancer patients, though experts stress that few people who take pain medications for cancer become addicted to the medications.

Many women in the study avoided or discontinued pain medication out of fear of side effects. At the same time, some participants wanted to learn about alternative and nontraditional approaches to pain management.

The women also wanted to learn about the pain experiences of others. "People were seeking out others for support, as well as for validation that their own pain was typical or normal," says Ms. Bender.

The participants' questions—in all, more than 200—may be relevant to other cancers and other diseases. The researchers, led by Dr. Alejandro R. Jadad of the Centre for Global eHealth Innovation at the University of Toronto and the University Health Network, are now looking at pain from the perspectives of patients with other chronic conditions, or who belong to different ethnic or cultural communities.

So far, the research has identified some core themes across the patient populations as well as themes that are specific to each group.

As a next step, the researchers are

(continued on page 8)

(Spotlight continued from page 7)

developing an interactive Internet tool that patients can use to explore questions about pain and communicate with other patients in pain before meeting with physicians and nurses.

"We see it as a clinical appointment preparation tool for people who have pain," says Ms. Bender, noting that patients and health professionals have to communicate effectively about pain. The Web site aims to help patients organize their questions so that they can be addressed during appointments.

Formulating questions about pain—or any health issue—is not easy, and patients worry that their questions may take more time than is allotted for a typical consultation.

"If pain is to be managed adequately, efficient mechanisms are needed to help patients identify and articulate their questions and get answers," the researchers wrote.

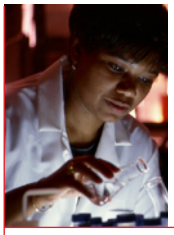
The Web site could certainly help, but real progress will involve all parties. Patients have to articulate their needs, while clinicians must create environments where people feel comfortable talking about their fears and concerns about pain.

"It is important to address pain from the very beginning of cancer treatment because unrelieved pain can further erode an already compromised quality of life," says Ms. Bender.

As more and more people survive cancer and return to productive lives, managing pain will be critical to ensuring a good quality of life for each one.

As one woman said, "I don't want pain to stop my life. I want to be able to live with it." ◆

By Edward R. Winstead



Featured Clinical Trial

Combination Therapy for Invasive Bladder Cancer

Name of the Trial
Phase I/II Study of Paclitaxel and Radiotherapy with or without Trastuzumab (Herceptin) in Patients Who Have Undergone Prior Transurethral Bladder Resection for Muscle-Invasive Transitional Cell Carcinoma of the Bladder (RTOG-0524). See the protocol summary at http://cancer.gov/clinicaltrials/RTOG-0524.

Principal Investigators
Drs. M. Dror Michaelson, Alan Pollack, and Douglas Dahl, Radiation Therapy Oncology Group

Dr. M. Dror Michaelson

Why This Trial Is Important
Complete removal of the bladder, or cystectomy, is the most common treatment for bladder cancer that has invaded the organ's muscle wall. However, to preserve the bladder and improve the quality of life for patients, doctors have developed a method for treating bladder cancer that uses a combination of chemotherapy and daily radiation therapy.

Previous clinical trials of this method have included only patients who were eligible for cystectomy, in the event that the bladder-preserving therapy failed. For patients who are not suitable for cystectomy, no standard treatment options currently exist.

In this trial, patients with invasive bladder cancer who are not suitable for cystectomy will be treated with the drug paclitaxel and daily radiation therapy. Also, patients whose tumors test positive for the protein HER2 will be treated with the monoclonal antibody trastuzumab (Herceptin).

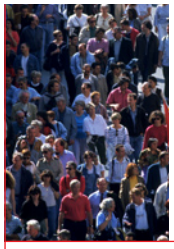
Some studies have suggested that 40–80 percent of bladder cancer tumors produce increased amounts of HER2 and that patients with such tumors tend to fare poorly compared to patients whose tumors do not overexpress this protein. Trastuzumab binds to HER2 on the surface of tumor cells and initiates a cytotoxic process.

"Patients with muscle-invasive bladder cancer who are not suitable for surgery have few options for treatment," said Dr. Michaelson. "With this trial we're testing what we hope to be a fairly gentle means of treatment using combination therapy developed for bladder preservation.

"In addition to trying to establish a safe and well-tolerated regimen that can be tested in larger clinical trials, we hope to clarify the role of HER2 in bladder cancer and determine if trastuzumab can help improve outcomes for patients whose tumors overexpress that protein," Dr. Michaelson added.

For More Information
See the list of entry criteria and trial contact information at http://cancer.gov/clinicaltrials/RTOG-0524 or call NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237). The call is toll free and confidential. ◆

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



Community Update

NIH to Begin Enforcing Public-Access Policy in April

Peer-reviewed journal articles based on NIH-funded research will soon become available to the public at no cost through the PubMed Central online database, which is administered by the NIH National Library of Medicine (NLM). This policy goes into effect on April 7 and will affect all intramural and extramural research funded in fiscal year 2008 and beyond.

"Public access is a public good," says Dr. Norka Ruiz Bravo, NIH deputy director of extramural research and director of the NIH Office of Extramural Research. "The mandatory policy makes publications resulting from NIH-funded research accessible to all—the public, health care providers, educators, and scientists, among others. Public access will help advance science and improve human health."

The policy is outlined at http://publicaccess.nih.gov and is legislated by the Consolidated Appropriations Act of 2008, which followed years of lobbying by proponents of public access and several intermediate Congressional bills.

It is estimated that approximately 80,000 journal articles each year are published as a result of NIH-sponsored research. Previously, study authors were asked to voluntarily submit their published manuscripts, but far fewer of them did than was hoped.

To enforce the new policy, NIH has instituted a condition in all grants and cooperative agreements such that, in accepting funds, researchers agree to submit their manuscripts to PubMed Central upon acceptance of publication. Articles can be embargoed for up to 12 months. After the embargo, however, the article will be made publicly available in PubMed Central.

More than 300 journals have an agreement with NLM where they automatically submit articles to PubMed Central, and the authors who want to publish in these journals need not do anything more. But if an author wishes to publish in another journal, they must submit the article themselves on the Manuscript Submission System (www.nihms.nih.gov). Beginning on May 25, authors must include a PubMed Central reference number for each article that they cite in their grant applications and proposals.

Retroactive submission of articles that were published before the April 7 deadline is not mandatory, but authors are encouraged to submit these manuscripts if they have appropriate copyright permission.

To assist intramural and extramural researchers with adherence to the new policy, the NIH Office of Extramural Research is planning a series of workshops in 2008. The office will announce these workshops on its Web site at http://grants.nih.gov/grants/oer.htm. ◆

Notice Anything New?

In this issue we've introduced a new icon. It indicates a topic or story idea suggested by a subscriber—in this case our Spotlight on cancer pain. Is there an issue or area of cancer research you'd like to read about in a future issue? Send us your feedback and ideas by clicking on the icon or writing to ncicancerbulletin@mail.nih.gov. We appreciate hearing from you, our readers, and continually strive to meet your needs. ◆

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.