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p53 Gene May Help Fight Tumors

Drug developers have long wondered whether *p53*, one of the most commonly mutated genes in cancer, would make a good target for cancer therapies. Three new studies in mice suggest that it might.

The gene normally helps suppress tumors, and many cancer patients are thought to acquire *p53* mutations relatively early in the disease. It has not been known whether these mutations also contribute to cancer later on, once tumors have been established.

The mouse studies suggest that they do. The researchers tested this idea by creating mice with *p53* genes that could be turned on and off. They allowed the mice to develop cancers before turning on the gene. When they activated *p53*, the results were dramatic.

Tumors disappeared as cancer cells died or stopped growing, sometimes within hours. In one study, mice with large tumors died because the anti-

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Director's Update

Guest Update by Dr. Dinah Singer

Dr. Dinah Singer
Director, NCI Division of Cancer Biology

Breast Premalignancy Research Bolstered by Database on Healthy Tissue

Developing a better understanding of the healthy breast is critical to our efforts to identify biomarkers and other diagnostic and therapeutic tools for use against early breast cancer. At last week's steering committee meeting of the NCI Breast Cancer Stamp Premalignancy Research Program, we heard about a new program that addresses the key issue of our limited understanding of the biology and normal developmental genetics of the mammary gland.

The "Friends for Life" project is an effort of the Indiana University (IU) Breast Program, the Catherine Peachey Fund, Inc., and the IU Cancer Center to create a collection of voluntarily donated breast tissue, blood, and macromolecules derived from blood and saliva of healthy donors. The undertaking is a collaboration among consumer advocates, clinicians, basic scientists, and volunteers. "Friends for Life" was created in response to a need articulated by scientists carrying out breast cancer research—in order to better under-

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(p53 *Genes continued from page 1)*
cancer response was so strong. Even restoring *p53* for a short time caused tumors to disappear.

"The tumors went away when we activated *p53*," says Dr. Scott Lowe of Cold Spring Harbor Laboratory in New York. His group studied mice with a form of liver cancer, and their results appeared online in *Nature* on January 24.

Each group used different methods to study different tumors. But they all concluded that at least some tumors depend for their survival on blocking the *p53* gene and the genetic program, or pathway, it controls.

"The *p53* pathway must be kept silent in established tumors for their viability," says Dr. Tyler Jacks of the Massachusetts Institute of Technology, who led a companion study in *Nature*. "The pathway appears to remain important even in advanced tumors."

If the same is true in human cancers, then a potential therapy may be to reactivate a damaged *p53* gene. The new results make this scenario seem plausible.

"The key point is that when you restore *p53* in established cancer cells, the gene is engaged in the pathway," says Dr. Gerard Evan of the University of California, San Francisco, who led the third study. Their findings appeared in *Cell* on December 29, 2006.

"This is incredibly good news because it means that mending a lesion in the *p53* pathway would restore the body's natural ability to kill or block the growth of tumors," says Dr. Evan.

The signals that activate *p53* and lead to an antitumor response are specific to cancer cells. This means that restoring *p53* is unlikely to have effects on normal tissues, and this was the case in most of the mouse experiments.

"These studies really do formally establish once and for all that the *p53* pathway is a good therapeutic target," says Dr. Lowe. Developing ways to restore defective genes in cells will not be easy, he adds, but efforts are underway.

The mechanisms by which the cancers regressed varied with the tumors. Dr. Jacks' team found that lymphoma cells died while sarcoma cells stopped growing. In Dr. Lowe's study, the immune system played a role in causing liver tumors to regress.

Dr. Evan's group provides a cautionary note—the lymphomas they saw regress eventually returned. But the researchers are learning why this happened, and they remain optimistic.

"I believe that restoring *p53* in human cancers is going to have a profound therapeutic effect that will be specific to cells with abnormal *p53*," says Dr. Evan. ◆

By Edward R. Winstead

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stand what is abnormal in breast cancer, the breast's normal state needs to be more clearly defined.

A partnership of patient advocates and clinicians eagerly accepted the challenge of developing a bank of normal tissue. The response of the community to the request for volunteers has been overwhelmingly enthusiastic. The tissue bank is currently the repository of more than 2,500 specimens collected over a 2-year period, including specimens from women participating in the annual Susan G. Komen "Race for the Cure" in Indianapolis. All specimens are annotated with detailed information about the donor; most are from women without evidence of breast cancer.

Dr. Anna Maria Storniolo, director of the Catherine Peachey Breast Cancer Prevention Program at the IU Cancer Center and the principal investigator on the project, described the three primary components of "Friends for Life:" 1) the blood and tissue collection procedures; 2) the repository of blood, DNA, and frozen human breast tissue which, in the future, will also contain plasma and RNA; and 3) a Web-based database that can be queried with regard to available specimens and the attributes of the specimens' donors.

This online database will be available later this year and will include additional information on the tissue bank, the standard operating procedures used for specimen collection, and instructions on how to request and obtain tissue.

The uses of normal breast tissue are myriad and include, for example, the isolation of RNA for gene microarrays, the inclusion of these tissues on tissue microarrays, and the cataloging of the epigenetic regulation of normal breast tissue. Annotated DNA from this project has already been utilized to identify single nucleotide polymorphisms associated with hot flashes.

The "Friends for Life" project is an important complement to NCI's Breast Cancer Premalignancy Program, which we think may lead to real advances in understanding and intervening in the early biological events associated with breast cancer premalignancy. ◆

Cancer Research Highlights

Arsenic Trioxide Improves Survival in Adults with APL

Recent results from a Cancer and Leukemia Group B (CALGB) phase III clinical trial showed that adult patients with acute promyelocytic leukemia (APL) who received arsenic trioxide (Trisenox) in addition to standard chemotherapy had significantly better event-free and overall survival than those who received only standard chemotherapy.

The NCI-sponsored CALGB study tested the effects of arsenic trioxide on 582 patients between June 1999 and March 2005. Patients with newly diagnosed APL, an uncommon form of leukemia, were randomly assigned to one of two treatment groups. The standard remission treatment group received the chemotherapy drugs daunorubicin and cytarabine with twice daily doses of all-trans retinoic acid (ATRA) followed by the standard postremission regimen of two more courses of ATRA plus daunorubicin. The experimental treatment group received the same standard treatment with the addition of two courses of arsenic trioxide given immediately after the patient entered a complete or partial remission and before the standard postremission regimen.

The researchers found that 77 percent of those adult patients in the combined chemotherapy and arsenic trioxide treatment group remained in remission 3 years after diagnosis compared to 59 percent of patients receiving only the standard treatment. In addition, 86 percent of adult patients on the combined chemotherapy and arsenic trioxide treatment regimen were still alive after 3 years compared to 77 percent of patients on the standard treatment.

Study co-investigator Dr. Richard Larson from the University of Chicago noted, "These results indicate that arsenic trioxide should be considered as part of the initial treatment of patients with acute promyelocytic leukemia."

Radiation After BCS Benefits Older Women with Breast Cancer

A study from the NCI-sponsored Cancer Research Network published online in *Cancer* on January 22 has shown that women aged 65 or older who receive radiation therapy after breast-conserving surgery (BCS) and 5 years of tamoxifen therapy have a reduced risk of cancer recurrence compared with those who do not receive these standard treatments.

Investigators led by Dr. Ann M. Geiger of Wake Forest University searched the medical records at six HMOs in the Cancer Research Network for women aged 65 or older who underwent surgery for early-stage breast cancer between 1990 and 1994. They recorded whether women had a full mastectomy, BCS followed by radiation therapy, or BCS alone. They also recorded the incidence and duration of tamoxifen use in women with hormone-receptor-positive tumors.

After adjusting for known prognostic variables, the investigators found that women who underwent BCS without radiation therapy had an increased risk of recurrence or second primary breast cancer compared with women who had a full mastectomy. In contrast, women who received radiation therapy in addition to BCS did not have an increased risk of either recurrence or a second primary cancer. Women with hormone-receptor-positive tumors who received 5 or more years of tamoxifen therapy were less likely to have a recurrence or second primary cancer than women who received tamoxifen for less than a year.

Radiation therapy following BCS and tamoxifen benefited women regardless of age, race, ethnicity, or comorbidities. Because several recent studies have shown that older women are less likely to receive standard cancer therapies, the authors stress "the importance of providing high-quality cancer care to all patients, regardless of age."

Study Confirms Cigarettes Packing More Nicotine Punch

Cigarette smoke-nicotine yields increased 11 percent between 1998 and 2005. That is the conclusion of a new report from the NCI-supported study by the Tobacco Research Program at the Harvard School of Public Health (HSPH), which analyzed data from the nation's major tobacco manufacturers.

The new report echoes findings from a similar report released last summer by the Massachusetts Department of Public Health. Massachusetts law requires all manufacturers of cigarettes sold in the state to provide a comprehensive annual report on

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nicotine yield and other measures of cigarettes design. Smoke-nicotine yields are measured using a standardized machine-generated method that compares cigarettes, regardless of individual smoking behavior.

The researchers identified two ways the cigarette manufacturers appear to have increased the smoke-nicotine yield: a higher concentration of nicotine in the tobacco rod (the portion of the cigarette that holds the majority of the tobacco) and a reduced "burn rate," which permits more puffs per cigarette. The researchers cautioned that these two factors could not account for the total increase seen and that "precise information about these products remains shrouded in secrecy, hidden from the public."

"Our findings call into serious question whether the tobacco industry has changed at all in its pursuit of addicting smokers since signing the Master Settlement Agreement of 1998 with the State Attorneys General. Our analysis shows that the companies have been subtly increasing the drug nicotine year by year in their cigarettes, without any warning to consumers since the settlement," said the study's lead author, Dr. Gregory Connolly, a professor of the practice of public health at HSPH.

The study authors note that "all cigarettes are highly addictive and deadly, and relatively minor changes in nicotine yield may not significantly alter the product's addictive properties." They suggest that the increased nicotine may be intended to make it easier for smokers to maintain their addiction, including lower income smokers who may be smoking fewer cigarettes as the price of tobacco products increases.

Women May Be Quitting Tamoxifen More Often than Thought

When women who have early-stage, hormone-responsive breast cancer take adjuvant tamoxifen for 5 years, it can dramatically reduce their risk of breast cancer recurrence and death. But sometimes women stop the treatment early and forgo these benefits. A study published online January 22 in *Cancer* reveals that the number of women who do this may be higher than previously thought.

Researchers at St. James's Hospital in Dublin analyzed records from a national database that logs prescriptions filled through the Irish government's free health care system, which serves approximately one-third of the country's population. The final study cohort included 2,816 women over the age of 35 who had filled tamoxifen prescriptions between January 2001 and January 2004.

Previous studies have estimated the rate of nonpersistence, or discontinuing treatment with tamoxifen, at between 16 and 32 percent within 5 years. The current study, which is the largest thus far, showed that the discontinuation rate was 35.2 percent after a follow-up of just 3.5 years. "It is likely that persistence with tamoxifen will have declined further by the time the cohort of patients in this study has completed 5 years of treatment," the authors warn. Some factors associated with nonpersistence included younger age (under 44) and older age (over 75).

The authors speculate that younger women may have difficulty accepting a diagnosis of breast cancer and thus may be less accepting of tamoxifen's side effects. They also note that because some types of antidepressants have been shown to decrease severe hot flashes, these drugs may improve persistence by minimizing side effects.

SWOG Closes Prostate Cancer Trial

The NCI-sponsored Southwest Oncology Group (SWOG) last week announced that it has closed a phase III prostate cancer treatment clinical trial because the new treatment under investigation was associated with a rare but dangerous side effect.

The trial, dubbed S9921, was designed to see whether hormone-deprivation therapy combined with the chemotherapy drug mitoxantrone was superior to hormone-deprivation therapy alone in men with "poor risk" prostate cancer—that is, cancer that had spread beyond the prostate and was at high risk of recurring after surgery or radiation therapy.

Mitoxantrone has already been approved by the Food and Drug Administration for the treatment of advanced prostate cancer. Of the 983 patients enrolled in the trial, 488 had received mitoxantrone as part of their treatment. In the most recent review of survival and side-effect data from the trial, SWOG explained in a statement, trial leaders noted three cases of acute myelogenous leukemia among the patients who had received mitoxantrone. No patients in the hormone deprivation-only group developed leukemia.

Following a review and recommendation from SWOG's Data Safety Monitoring Committee, the trial was closed. ◆

Spotlight

CA125: Biography of an Ovarian Biomarker

Epithelial ovarian cancer is known as the "deadly disease that whispers." Deadly because less than 30 percent of these cancers are detected in stage I when they are confined to the ovaries, highly treatable, and curable in up to 90 percent of patients; whispering because its early symptoms can be ambiguous or nonexistent.

For most ovarian cancer patients, however, the disease has begun to spread by the time it is detected, and only one in four patients with advanced ovarian cancer will be alive 5 years after diagnosis.

Ovarian cancer also provides the context for another story: the role of biomarkers in cancer research. A cancer biomarker is a substance in the body that—by its presence, pattern, or behavior—alerts clinicians to hidden biologic activity that might be associated with some aspect of the precancerous or neoplastic process.

For many years, a protein known as CA125 has been a prominent blip on researchers' radar screens. The history of CA125 illustrates the promise and the challenges involved in the search for a biomarker that could lead to meaningful clinical progress in fighting ovarian cancer.

The Early Years

After the development of monoclonal antibody technology in 1975, many scientists began the search for antibodies that would react with specific tumor tissue types. One of those researchers was Dr. Robert C. Bast, who would go on to become vice president for translational research and the principal investigator for the Ovarian SPORE at the University of Texas M.D. Anderson Cancer Center.

In the late 1970s, Dr. Bast and colleagues used the then new monoclonal technology to develop antibodies against human ovarian cancer, and their 125th hybridoma produced an antibody that would bind to antigens expressed by about 80 percent of epithelial ovarian cancers (which comprise about 90 percent of all ovarian cancers). They named it OC-125 and by 1983 Dr. Bast's group reported the first clinically usable, monoclonal antibody radioimmunoassay to monitor the response of epithelial ovarian cancer to treatment, known as the CA125 test.

Equipped with a test for an antigen that epithelial ovarian cancer cells shed into the blood, researchers wondered if they had a potential screening test.

"To stand alone as a screen for ovarian cancer, a biomarker would have to detect significantly more cases at the early, highly curable stage than the 28 percent we find now. We need a sensitivity of at least 80 percent," says Dr. Beth Karlan.

Dr. Karlan is director of the Gilda Radner Hereditary Cancer Detection Program at Cedars Sinai's Women's Cancer Research Institute in Los Angeles. Since a positive test could lead to abdominal surgery, its positive predictive value needs to be at least 10 percent. "You also want to avoid false-positives in a relatively rare disease, and so the specificity should exceed 99 percent," she explains.

The CA125 test did not meet this threshold, in part because elevated CA125 levels were also found in patients with other types of cancer, and also in several benign conditions; only about 3 percent of patients with elevated CA125 actually had previously undetected ovarian cancer. "Nonetheless we knew we had a potential tool, it was just a matter of learning how to use it," notes Dr. Bast.

Coming of Age

"A prognostic biomarker is something we can measure that correlates to disease outcome," explains Dr. Gary Kelloff, special advisor to NCI's Cancer Imaging Program in the Division of Cancer Treatment and Diagnosis. "If a cellular protein like CA125 can stand in as an effective surrogate for the standard way we measure how ovarian cancer responds to chemotherapy, it could economize and hasten the process of testing new drugs."

In advanced ovarian cancer, surgery to remove all detectable disease is the first-line treatment, usually followed by chemotherapy administered directly into the peritoneum. Unfortunately, most patients eventually see their disease recur and progress. The standard way to mark such recurrence is the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, which rely on imaging to detect a visible mass.

"But when ovarian cancer does recur, CA125 sends us a message about 3

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months before we could detect it in any other way," says Dr. Bast.

Since the late 1980s, Dr. Gordon J.S. Rustin has been conducting a series of clinical trials on how to translate this early warning signal most accurately, since many clinicians were monitoring CA125 levels but interpreting them differently. The Gynecologic Cancer Intergroup (GCIG), formed in 1997, joined many of the cooperative groups into a common organization to foster collaboration and consensus.

By 2006, GCIG had agreed on definitions for measuring response and progression. While there may still be a few final issues to resolve, Dr. Rustin believes it is crucial to have the most accurate early date of progression established uniformly in clinical trials. He and others are working to validate the GCIG standard. "A comprehensive analysis of emerging data on CA125 may lead regulatory agencies to adopt it into their thinking about drug development and drug approval," says Dr. Kelloff.

A Crucial Tool

The CA125 assay has twice been refined, and now serves as a versatile tool for ovarian cancer clinicians. It fills several important roles, not to mention its revived prospects as part of a multistep screening approach.

Transvaginal ultrasound (TVU) and color power Doppler imaging can sometimes distinguish a benign from a malignant pelvic mass. A new model incorporates CA125 levels into an imaging approach that has a specificity of greater than 99.6 percent and a sensitivity of more than 70 percent in detecting malignancy, providing the required 10 percent predictive value.
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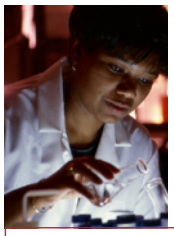
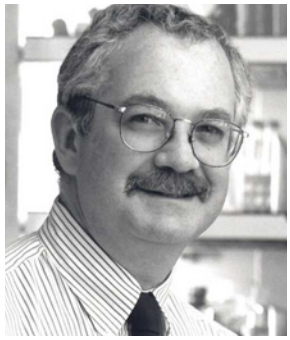


Featured Clinical Trial

Sorafenib for Kaposi's Sarcoma

Name of the Trial
Phase I Study of Sorafenib in Patients with Kaposi's Sarcoma (NCI-06-C-0083). See the protocol summary at http://cancer.gov/clinicaltrials/NCI-06-C-0083.

Principal Investigator
Dr. Robert Yarchoan, NCI Center for Cancer Research


Dr. Robert Yarchoan

Why This Trial Is Important
Kaposi's sarcoma (KS) is a type of cancer characterized by the abnormal growth of blood vessels and lesions in the skin and some internal parts of the body. KS is the most common cancer associated with acquired immunodeficiency syndrome (AIDS). There are several other forms of KS, including one (classic KS) that usually develops in elderly men of Mediterranean or Jewish descent and one (endemic KS) that occurs in Africa.

Because blood vessel growth is a central component of KS tumors, researchers believe that drugs targeting blood vessel growth may be effective in treating KS. In this trial, patients with either AIDS-related or non-AIDS-related KS will take varying doses of the drug sorafenib (Nexavar) for up to 54 weeks. Sorafenib is a new type of targeted drug that blocks the activity of several proteins that are important for cell division and for the growth of new blood vessels (angiogenesis).

Researchers will examine the safety of the drug and determine how the drug is processed in patients with KS who are receiving antiretroviral therapy for human immunodeficiency virus (HIV) infection and in those who are not receiving such treatment. Certain protease inhibitors that are used to treat HIV can affect the metabolization of sorafenib.

"Sorafenib blocks several molecular pathways important for the growth of KS," said Dr. Yarchoan, "so we have a good rationale for using this FDA-approved drug [for kidney cancer] in patients with KS. Additionally, we are exploring the potential interactions between sorafenib and the antiretroviral drug ritonavir, which is often used to treat patients infected with HIV-1."

Who Can Join This Trial
Researchers seek to enroll 45 patients aged 18 or over with either AIDS-related or non-AIDS-related KS. See the list of eligibility criteria at http://cancer.gov/clinicaltrials/NCI-06-C-0083.

Study Site and Contact Information
This study is taking place at the NIH Clinical Center in Bethesda, MD. For more information, call the NCI Clinical Trials Referral Office at 1-888-NCI-1937. 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.

Notes

Dr. Sanya A. Springfield Appointed Director of CRCHD

Dr. Sanya A. Springfield was recently appointed as the director of NCI's Center to Reduce Cancer Health Disparities (CRCHD). Dr. Springfield, who has served as acting director of CRCHD since the fall of 2005, will continue sustaining CRCHD's mission to lessen the burden of cancer on the most vulnerable populations. Her goals are to leverage resources through collaborations and partnerships, to generate cancer health disparities research at NCI, and to train first-generation cancer health disparities researchers.

Prior to joining CRCHD, Dr. Springfield served as chief of NCI's Comprehensive Minority Biomedical Branch where she led activities to increase the number of competitive minority researchers involved in cancer research, including the Continuing Umbrella of Research Experiences program.

caBIG Annual Meeting Slated for February

The 2007 annual meeting of NCI's cancer Biomedical Informatics Grid (caBIG) will be held February 5–7 at the Marriott Wardman Park in Washington, DC. The meeting provides a forum for the exchange of the latest knowledge in the ongoing creation of a "World Wide Web of cancer research." The meeting will feature more than 100 scientific presentations, technology demonstrations, and interactive sessions on caBIG activities.

There is no charge for the conference, but participants should register on the meeting Web site, https://cabig.nci.nih.gov/2007caBIGconference, if they plan to attend. ◆

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_013007/page8 ◆

70 YEARS OF EXCELLENCE IN CANCER RESEARCH

If Memory Serves…

The NIH campus was erected in Bethesda, MD, on 45 acres of land that had been donated to the government by Mr. and Mrs. Luke Wilson. Upon passage of the National Cancer Institute Act in 1937, Mrs. Wilson, whose husband had died of cancer, donated an additional 10 acres for the construction of NCI's first building, Building 6, the cornerstone of which was laid on June 24, 1939. ◆

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

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Tumor response and progression are also markers of a patient's prognosis that CA125 testing can measure. The half-life of CA125 is about 14 days following initial surgical resection and the beginning of chemotherapy. Persistent disease that may not be detected by imaging, however, extends this time to more than 20 days, correlating with a poor prognosis.

Dr. Kelloff suggests that CA125 could play an important role in clinical trial design. For example, when used in all arms of a randomized trial, CA125 could signal an earlier time to stop ineffective drug combinations.

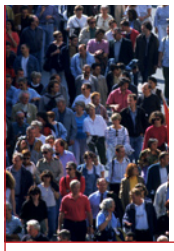
"The potential value is great," adds Dr. Rustin. "Patients identified by CA125 can be included in phase II trials, even though they would not have qualified using RECIST. The go/no-go decisions to keep drugs moving through the pipeline can be reached more quickly and economically in many cases."

And back to screening, where it all began for CA125. "Currently, we combine CA125 and TVU and focus on women with a strong family history of ovarian cancer or early-onset breast cancer," says Dr. Karlan. NCI's large PLCO clinical trial is investigating these two screening tests in a general population of older women.

Molecular and genetic research is starting to uncover more specific signatures of the early stages, says Dr. Karlan, who credits NCI's Early Detection Research Network for useful guidelines to develop new biomarkers for screening.

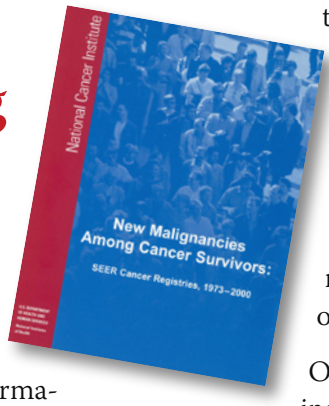
"I expect an effective screen for ovarian cancer to emerge by 2015," predicts Dr. Bast. "And when it does, CA125 may still be one of its integral features." ◆

By Addison Greenwood



Community Update

Monograph Highlights New Malignancies Among Cancer Survivors



Researchers from NCI's Division of Cancer Epidemiology and Genetics (DCEG) and Division of Cancer Control and Population Sciences (DCCPS) recently published a monograph, *New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973–2000*. The monograph is the first publication to provide a comprehensive analysis of the risk for U.S. cancer survivors of developing a new malignancy.

"This is by far the largest study to date to assess risk of subsequent cancers. It includes more than 2 million cancer survivors during a nearly 30-year period and more than 185,000 subsequent primary cancers," said lead editor Rochelle Curtis of DCEG's Radiation Epidemiology Branch. "Other studies have evaluated risk of subsequent cancers for individual cancer types or groups of cancers, usually related to the late effects of treatment, but this report provides the first complete evaluation of subsequent cancer risk in the U.S. for most first primary cancer sites."

The report used data from nine cancer registries participating in the Surveillance, Epidemiology, and End Results (SEER) Program from 1973 to 2000.

"This report adds a new dimension to cancer surveillance in that it pinpoints which cancers are more likely to be followed by another primary. This knowledge is possible because of the depth of information from almost 30 years of consistently reliable SEER data," noted co-editor Lynn Ries of DCCPS's Cancer Statistics Branch.

More than 50 adult and 18 childhood cancers were evaluated in the new report, which includes new data on less common cancer sites. More than 350 data tables present the risk of subsequent cancer by time since initial diagnosis, sex, age at initial diagnosis, and when appropriate, by treatment and cancer cell type. Each chapter compares the findings with other published studies and discusses the results in terms of potential risk factors and mechanisms.

Overall, the results showed that cancer survivors have a 14-percent increased risk of developing a subsequent cancer than would be expected in the general population. Many of the patterns of multiple cancers suggested an effect of shared risk factors (such as tobacco and alcohol consumption, nutritional factors, hormones, infections and immunosuppression, and genetic predisposition) or a carcinogenic effect of cancer therapies. Although a sizable portion of multiple cancers in the SEER database represented tumors that occurred in the same or neighboring organ systems, most of the subsequent cancers occurred in diverse organ sites.

One of the most striking findings was that tobacco smoking, excess alcohol intake, or the interaction of the two exposures appeared to account for more than 35 percent of the excess cancer risk observed in the survivor population.

"This effort represents an important collaboration between two NCI divisions," said Dr. Joseph F. Fraumeni, Jr., DCEG director and senior editor of the monograph. "It should provide a tremendous resource for clinicians, researchers, and other health professionals, and it should be useful in alerting cancer survivors to the importance of medical supervision for prevention and early detection of new malignancies."

The monograph may be viewed or ordered at http://seer.cancer.gov/publications/mpmono/. ◆

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.