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NCI Cancer Bulletin

Eliminating the Suffering and Death Due to Cancer

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Large Portion of Late-Stage Breast Cancers Associated With Absence of Screening

Increasing mammography screening rates and investing in research to improve breast cancer detection technologies should be top priorities, according to authors of a study published in the October 20 *Journal of the National Cancer Institute*. As many as 92 percent of late-stage breast cancer cases in the United States could be diagnosed and treated earlier, when there is greater likelihood of effective treatment, if the healthcare system focused on recruiting women who have not been recently screened, and if early detection techniques could be improved to more accurately detect cancer. The study was conducted by researchers at the National Cancer Institute (NCI), part of the National Institutes of Health (NIH), and the Cancer Research Network, a consortium of integrated health plans.

For more information on the Cancer Research Network, a consortium of integrated health plans, visit http://crn.cancer.gov/

Study results indicated that not having had a screening mammogram for 1 to 3 years prior to diagnosis was associated with 52 percent of late-stage

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Director's Update

Nutrition: A New Frontier in Cancer Research

The obesity epidemic has generated intense concern in the medical community, and rightfully so. It has had devastating consequences for our nation's health and health care system, driving rates of several chronic illnesses into the stratosphere and heaping tens of billions of dollars onto an already strained health care budget. And as we are beginning to better appreciate, obesity has also significantly affected cancer incidence, progression, and death rates. In fact, the most recent estimates attribute 3.2 percent of all new cancers—14 percent of cancer deaths in men and 20 percent in women—to obesity.

NCI, on its own and in partnership with other HHS agencies, is focused on better understanding the link between obesity and cancer and, at the same time, working to minimize the epidemic's impact. We are also beginning to better understand that the influence of diet on cancer goes well beyond questions of quantity and energy expenditure.

To be sure, the food we eat every day is remarkably complex. Its nutrients and molecules have profound genetic and cellular effects that directly influence cancer susceptibility. The

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breast cancer cases. The authors state that to improve breast cancer outcomes, priority should be placed on reaching unscreened women and encouraging them to have mammograms—especially older, unmarried, less educated, and/or low income women, whom they found were less likely to have been screened. "The good news is that there is a lot known about how to reach women who have never been screened or who fail to get regular mammograms," said Dr. Stephen Taplin, a senior scientist in NCI's Division of Cancer Control and Population Sciences and lead author of the study. "The challenge is to put this knowledge into practice."

The study was based on a review of all medical care received by 2,694 women during the 3 years prior to their breast cancer diagnosis. Researchers reviewed medical charts and records of women in seven integrated healthcare plans across the United States. The plans offer specialty and primary care within the same system, and serve 1.5 million women over age 50. All offer breast cancer screening mammograms at no or low cost. When the study began in 1999, 71 to 81 percent of these women had gotten mammograms. "Few women in a regularly-screened population should be diagnosed with late-stage breast cancer because, in theory, screening should identify cancers before they progress to the late stage," explained Taplin. "However, there were still cases of late-stage breast cancer in this population."

Women who had not been screened 1 to 3 years prior to diagnosis were more than twice as likely to have late-stage breast cancer. This illustrates an important reason for receiving regular mammograms: to increase the chance of catching breast cancer early. However, a second finding showed that better screening tests need to be developed. Almost 40 percent of women with late-stage breast cancer had a negative mammogram 1 to 3 years before their diagnosis.

In response to this study, NCI Director Dr. Andrew C. von Eschenbach stated, "This study helps us identify research priorities for breast cancer screening. To eliminate the suffering and death due to cancer, we need to improve delivery to reach women who don't receive regular mammograms, improve the interpretation of mammography, and find new screening tests. All these things are important to achieve national goals." ◆

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components of our daily diet—the calcium in milk, the zinc in chicken and nuts, the flavonoids in onions and carrots, the fatty acids in tuna or avocados—all alter a broad array of cancer-related events, including inflammatory response, carcinogen metabolism, cell death, and DNA repair.

The Nutrition Sciences Research Group (NSRG) in the NCI Division of Cancer Prevention, led by Dr. John A. Milner, is an important leader in this field of investigation, conducting and funding research aimed at detailing and further characterizing the delicate relationship between diet and cancer. We are becoming increasingly aware, for example, that genetics can affect the function of bioactive food components. Epidemiologic studies have shown that in patients with specific genetic polymorphisms that influence chromosomal stability, adequate levels of folate—a component of leafy vegetables and a nutrient often used to fortify processed foods such as breakfast cereals—likely decreases the risk of colorectal cancer. To further investigate the link between folate and colorectal cancer, NCI is funding a number of studies, including an effort being led by investigators at Harvard, Dartmouth, and Tufts by Dr. David J. Hunter to further elucidate the pathways through which folate may affect colorectal cancer risk and the influences of specific genetic mutations in determining that risk.

Importantly, some of the advanced technologies we are using in many areas of cancer research—including microarray analysis, nanotechnology, metabolomics, proteomics, and bioinformatics—may provide nutritional scientists with some valuable new tools, allowing them to identify molecular sites of action of bioactive food components, diagnose a person's nutritional status, and mine the flood of genomic data now available to more quickly identify those foods and compounds with the greatest cancer prevention properties.

However, each one of us is unique and has slight genetic variations: That means some of us respond to certain bioactive food components and some don't. As Dr. Milner stresses in his talks and published papers, our challenge is to ensure that we communicate the importance of collecting the genomic data needed to make understanding these differences a reality.

I'm confident this work will go a long way toward identifying appropriate dietary intervention strategies to reduce the risk of developing cancer and perhaps even change the behavior of existing malignant cells. Armed with a greater understanding of how obesity and diet influence cancer risk, we can look to a day where diet fads and crazes are supplanted by rational, evidence-based recommendations that promote true health and wellness. ◆

Dr. Andrew C. von Eschenbach
Director, National Cancer Institute

Cancer Research Highlights

Birth Weight, Childhood Growth, and Breast Cancer

In women, body size has been correlated with risk for breast cancer. Obese women, for example, have a lower risk before menopause and higher risk after, and tall women are generally at higher-than-average risk for breast cancer. Now, researchers at the Danish Epidemiology Science Center and Copenhagen's Institute of Preventive Medicine have traced these trends back to adolescence and childhood. This research, supported by the U.S. Department of Defense Congressionally Directed Medical Research Programs, the Danish Medical Research Council, the Danish National Research Foundation, and the Danish Cancer Society, is published in the October 14 *New England Journal of Medicine*.

Danish schools track students' birth weight; annual weight and height; and, for girls, age at first menstrual period. These records are entered in a civil registration system and can be linked with registries for cancer patients. In this study, researchers examined medical records from a cohort of Danish women who attended school in Cophenhagen and were born between 1930 and 1975, 117,415 of whom had complete records on height and weight at 8, 10, 12, and 14 years of age, and 3,340 of whom eventually developed breast cancer. A comparison of these cases with a control group of 5,500 medical records showed that the risk for breast cancer, after adjusting for body mass index (BMI), correlates directly with birth weight, with height at 8 years of age, and with growth rate between the ages of 8 and 14 years, but correlates inversely with BMI at age 14.

The study authors suggest that timing of breast differentiation may be a factor in these trends, noting that puberty marks the start, and first pregnancy the final stage, of breast cell differentiation—a point at which they become more resistant to carcinogenesis. "Overall," the authors write, "our results provide evidence that factors influencing fetal, childhood, and adolescent growth are important independent risk factors for breast cancer in adulthood."

Fruit, Vitamin C Protect Against Stomach Cancer

New data from a large prospective nutrition study indicate that a diet high in fruit may protect against the most common form of stomach cancer. The findings—presented by NCI researchers on Oct. 17 at the American Association for Cancer Research's (AACR) "Frontiers in Prevention" conference—showed that, at 12 years follow-up, a diet high in fruit and vitamin C, as well as gamma-tocopherol, a form of vitamin E, and lycopene, an antioxidant found in high concentrations in tomatoes, were protective against gastric noncardia cancer (GNCC). The strongest preventive associations were for fruit and vitamin C consumption.

"These results confirm findings on fruit and vitamin C from many other studies," said one of the study's lead investigators, Dr. Farin Kamangar, a visiting fellow in the NCI Center for Cancer Research (CCR). "As a result, we believe that fruit and vitamin C are likely to be useful for the prevention of stomach cancer. As for lycopene, we need to wait for further results that confirm these findings before we can say whether there is sufficient evidence of a protective effect."

The report offers the most recent findings from the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, led by NCI and the Finland Institute of Public Health. The study, conducted from 1985–1993, involved more than 29,000 male Finnish smokers and initially focused on lung cancer prevention. In this recent analysis, despite the apparent positive effects of gamma-tocopherol in preventing GNCC, high dietary intake of gamma- and alpha-tocopherol were associated with a slightly elevated increased risk of the less-common form of stomach cancer, gastric cardia cancer. The finding that different antioxidants have disparate effects according to gastric cancer type, Dr. Kamangar and colleagues concluded, should be taken into account in the design of future prevention trials.

Inactivating MYC Gene Returns Liver Tumor Cells to Normal Function

Some liver cancer tumor cells return to their normally functioning states and liver tumors undergo significant regression when a single oncogene is inactivated, according to a study published online on October 10 by *Nature*. Working in a transgenic mouse model of hepatocellular carcinoma, a form of liver cancer that

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Spotlight

Folkman Optimistic About Angiogenesis Research

"As cancer treatments become more targeted and less toxic, how much earlier can we treat cancer and what difference will it make?"

Speaking October 5 at the NCI CCR grand rounds, Dr. Judah Folkman, Andrus Professor of Pediatric Surgery at Children's Hospital in Boston and professor of cell biology at Harvard Medical School, used this question to frame his talk on whether the "angiogenic switch"—in which tumors gain the ability to recruit a blood supply and grow—can be prevented.

"There's an enormous amount of data that says when you are diagnosed with cancer, it has been on the way for many years," he said. Given that reality, he asked, are clinicians and the research community missing an opportunity by using angiogenesis inhibitors in the same way clinicians use other treatment modalities—only after patients have symptoms, the tumor is located, and has started to cause damage? The available genetic and clinical evidence on angiogenesis inhibitors, Dr. Folkman argued, suggests that they could be used to prevent tumors from ever forming or to keep small, harmless tumors in check.

In a study published in *Cancer Cell* last year, for instance, researchers showed that if just one angiogenesis inhibitor, tumstatin, was knocked out in wild-type mice, tumor growth increased by 400 percent. However, adding back physiologic levels of tumstatin returned the tumor to its baseline growth rate; increasing those levels shrunk tumors even further. Dr. Folkman also pointed to research on patients with Down syndrome who, with the exception of testicular cancer, almost uniformly fail to get solid tumors. A study in the *European Journal of Human Genetics* in 2001 appears to explain why. In the study, researchers found that, compared with normal controls, people with Down syndrome had twice the levels of the angiogenesis inhibitor endostatin, a cleavage product of collagen VIII whose gene is present on chromosome 21. (Down syndrome patients have an extra copy of chromosome 21.)

To date, Dr. Folkman noted, his lab has identified three angiogenesis-based biomarkers. Using imaging techniques that take advantage of luciferase, the lab has been able to view tumors down to 100 microns and actually measure when a tumor jumps to an angiogenic phenotype. "For the first time now," he said, "we can see the angiogenic switch, measured by light flux, 3 weeks before you can palpate a 50-millimeter tumor." ◆

(Research Highlights continued from page 3)
often fails to respond to existing treatments, Stanford University researchers found that when the MYC oncogene was inactivated with the antibiotic doxycycline, not only did the tumors completely regress in 30 days, but some tumor cells also resumed normal function. "Upon MYC inactivation, most of the liver tumor cells are able to differentiate into hepatocytes and biliary cells, forming bile duct structures," the researchers wrote.

To confirm that MYC inactivation was indeed responsible for this activity, the research team, led by Dr. Dean W. Felsher, and funded in part by NCI, reactivated the gene. The result: tumor growth resumed. Using a technology known as array comparative genomic hybridization, the researchers determined that the newly active tumor cells were genetically identical to those that had become dormant after MYC inactivation.

The researchers cautioned that "liver cancer may respond differently than other tumors to oncogene inactivation, because the liver has the intrinsic ability to regenerate itself, demonstrating that the liver maintains stem cells." Because the liver tumor cells "retained the ability to differentiate into multiple hepatic lineages," they argued, these particular cells may represent "dormant cancer stem cells." ◆

NCI Director to Address Asian Americans

NCI Director Dr. Andrew C. von Eschenbach will deliver the keynote address and meet with members of the Asian American media during the 5th Asian American Cancer Control Academy to be held in Sacramento this week, October 22–23. On Thursday, October 21, before the conference opens, Dr. von Eschenbach will also be interviewed by the *Sacramento Bee* on American cancer control efforts and disparities initiatives in the context of the 2015 challenge goal.

The 2-day conference is a meeting of the Asian American Network for Cancer Awareness, Research and Training (AANCART). This conference brings together cancer control authorities from throughout the country to discuss Asian American cancer incidence and mortality trends, smoking rates, and diet and exercise patterns, with an emphasis on the Hmong community.

In the Asian American community, cancer is the leading cause of death for women, unlike all other racial and ethnic groups, in which cardiovascular disease is the leading cause of death. For example, cervical cancer rates are five times higher for Vietnamese American women than for white women.

AANCART is a cooperative agreement between NCI and the University of California, Davis, and is the first national cancer awareness research and training entity for addressing the cancer concerns of Asian Americans. It is also a component of NCI's Special Populations Network. ◆

NIH Update

Roadmap Progress Faster Than Anticipated, NIH Director Tells Staff

A series of multi-disciplinary and inter-disciplinary networks and centers, along with innovative training programs, biocomputing centers, and grant funding for creative-thinking scientists, are among a comprehensive package of strategic funding initiatives being implemented as part of the National Institutes of Health's (NIH) Roadmap for Medical Research takes shape. This was reported by NIH Director Dr. Elias Zerhouni to employees and partners in a campuswide update on October 14 at Lipsett Amphitheater.

"I think we need to bring good ideas to the table…to stake the ground where science is going to go in the 21st century," Dr. Zerhouni said in his remarks. He reported that early returns from stakeholders show that initial implementation of the Roadmap is being well-received, and it is bringing more "logic and focus" to NIH's research initiatives with "enormous and amazing speed."

Dr. Zerhouni unveiled the Roadmap strategy last year, saying that NIH in the 21st century must "accelerate the pace of discovery" and improve research efficiency. The overarching goal is to move NIH toward a culture of "team science," where NIH researchers from various disciplines work collaboratively and creatively across organizations and disciplines.

The implementation of the Roadmap is occurring along three tracks: New Pathways to Discovery, Research Teams of the Future, and Re-engineering of the Clinical Medical Enterprise. Approximately $129 million in Roadmap projects were funded in fiscal year 2004 in each of these three categories.

In the category of New Pathways to Discovery, NIH is developing a "toolkit" that will help scientists better understand how biological systems work, including providing a detailed look at the combination of molecular events leading up to disease. The priorities for this are building blocks, biological pathways, and networks; molecular libraries and molecular imaging; structural biology; bioinformatics and computational biology; as well as nanomedicine. In addition to funding an initial group of National Technology Centers for Networks and Pathways aimed at encouraging the development of highly novel technologies in proteomics, other NIH projects reported include:

- A *Small Molecule Repository* to acquire, maintain and distribute up to 50,000 compounds with diverse chemical structures and known or unknown biological activities
- A *Molecular Libraries Screening Centers Network* that will provide public and private researchers with small molecules and be linked to a larger database of biological information on small organic molecules (PubChem)

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NIH Update

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- *High-Throughput Molecular Screening Assay Development* to create a continuous stream of biological assays that can be used for automated screening at the Molecular Libraries Screening Centers
- *National Centers for Biomedical Computing*, which will create a networked computational infrastructure for national biocomputing needs and help educate and train researchers to use biomedical computing

Under Research Teams of the Future, NIH is rewarding aggressive risk-taking by researchers, encouraging interdisciplinary research and enabling public-private partnerships. The new Director's Pioneer Awards highlight this area, with awards going to individual scientists with non-traditional approaches to biomedical research. The first group of recipients has already been chosen. Other Research Teams' projects include creating centers for interdisciplinary research and training programs for a new interdisciplinary workforce.

The third focus of the NIH Roadmap initiative is to Re-engineer the Clinical Research Enterprise, moving research from bench to bedside as efficiently as possible. Priorities include integrating and expanding clinical research networks and examining the feasibility of a National Electronics Clinical Trials/Research Network (NECTAR). ◆

Featured Clinical Trial

Study of Familial Testicular Cancer

Name of the Trial

Genetic and Etiologic Multidisciplinary Study of Familial Testicular Cancer (NCI-02-C-0178). See the protocol summary at http://cancer.gov/clinicaltrials/NCI-02-C-0178.

Principal Investigators

Dr. Mark H. Greene (protocol chair), Dr. Joan L. Kramer, and Dr. Mary L. McMaster, NCI Division of Cancer Epidemiology and Genetics, Clinical Genetics Branch

Principal Investigator Dr. Joan L. Kramer

Why Is This Study Important?

Testicular cancer is a relatively uncommon cancer, but one that has disproportionate importance because it affects young men in the prime of their reproductive and working years. The causes of testicular cancer are unknown, but evidence suggests that some people may have a genetic predisposition to developing this disease.

Researchers at NCI are studying families that have multiple cases of testicular cancer. Studying this population may lead to the identification of a gene or genes that make people more susceptible to testicular cancer.

"Our goal is to identify genes related to testicular cancer susceptibility and to define the full spectrum of conditions that are part of testicular cancer syndrome," said Dr. Kramer.

"Together with our colleagues in the International Testicular Cancer Linkage Consortium, we are trying to clarify the mechanism of testicular cancer risk in these families," Dr. Greene added.

Who Can Join This Study?

Researchers seek to enroll approximately 750 people aged 12 and over who have a familial history of testicular germ cell tumor. See the full list of eligibility criteria at http://cancer.gov/clinicaltrials/NCI-02-C-0178.

Where Is This Study Taking Place?

This study is taking place at the NIH Clinical Research Center in Bethesda, Md.

Who to Contact

For more information, visit the study Web site at http://familial-testicular-cancer.cancer.gov or call the NCI Clinical Studies Support Center (CSSC) at 1-888-NCI-1937. The CSSC provides information about studies taking place on the NIH campus in Bethesda, Md. 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

Report Shows Exercise is Key for Cancer Survivors

Exercise programs during and after cancer treatment can improve functional capacity and cardiopulmonary fitness, reduce symptoms of fatigue, and improve a patient's quality of life, according to a new report released in August by the Agency for Healthcare Research and Quality (AHRQ). The report, funded by NCI, also shows that exercise programs can reduce cancer patients' symptoms of anxiety and depression during treatment.

The study, led by researchers at the University of Minnesota's Evidence-Based Practice Center, looked at studies published between 1996 and 2003—specifically, studies that tested the effect of physical activity interventions, alone or combined with diet modification or smoking cessation, on cancer survivors. The results of this analysis did not favor any one type of exercise program or setting and showed no difference between shorter, less intensive programs and longer programs that were more intensive.

"Regular physical activity is important for both lowering the risk for and managing multiple diseases, including some cancers," commented NCI Director Dr. Andrew von Eschenbach. "The more we understand about how to help people start and maintain exercise programs, the more we can help cancer survivors combat some of the early and late effects of cancer and its treatment." The entire report is available at http://cancercontrol.cancer.gov/d4d/evidence_report.html.

Dr. Anita Roberts Wins 2005 FASEB Excellence in Science Award

Dr. Anita Roberts, principal investigator and former chief of the Laboratory of Cell Regulation and Carcinogenesis, has won the Excellence in Science Award from the Federation of American Societies for Experimental Biology (FASEB) for 2005. Sponsored by Eli Lilly and Company, this award recognizes outstanding achievement by women in biological sciences whose research has contributed significantly to further understanding of a particular discipline. In addition to presenting the award lecture at the Experimental Biology meeting in San Diego in April, 2005, Dr. Roberts will receive a $10,000 unrestricted research grant, funded by Eli Lilly and Company.

EGRP Holds Leadership Conference for Epidemiologists

NCI's extramural research program in epidemiology, the Epidemiology and Genetics Research Program (EGRP) recently held its first annual Epidemiology Leadership Workshop to identify barriers and gaps in cancer epidemiology and advance solutions to the study of tobacco, diet/energy balance, and genes. EGRP is part of NCI's Division of Cancer Control and Population Sciences (DCCPS) and manages a portfolio of 500 cancer epidemiology research grants totaling $200 million per year.

Drs. Edward Trapido, Catherine DeAngelis, and Robert Croyle

Dr. Catherine DeAngelis, editor-in-chief of the *Journal of the American Medical Association*, gave the keynote address on the importance of epidemiologic studies to public health. Other presentations were given by Dr. Laurence Kolonel, Cancer Research Center of Hawaii, University of Hawaii, on diet, genes, and cancer; Dr. Neil Caporaso, NCI's Division of Cancer Epidemiology and Genetics (DCEG), on tobacco, genes, and cancer; Dr. Stephen Chanock, DCEG and CCR, on genetics in epidemiology; Dr. Michael Thun, American Cancer Society, on cohort consortia; and Dr. Patricia Hartge, DCEG, on case-control consortia. Also speaking were Dr. Graham Colditz, Brigham and Women's Hospital, Harvard University; Dr. Margaret Spitz, University of Texas M.D. Anderson Cancer Center; and Drs. Robert Croyle, Jon Kerner, and Edward Trapido, DCCPS.

As a result of the workshop, four research working groups based on the breakout sessions' work will be formed: Diet/Energy Balance Epidemiology Research, Haplotypes versus Genotypes, Epidemiology of Rare Cancers, and Susceptibility to Tobacco Carcinogenesis. Extramural and intramural scientists will collaborate in the groups to generate new scientific ideas and hypotheses.

Participant presentations and more information about the workshop will be made available on the EGRP Web site at epi.grants.cancer.gov. ◆

CCR Grand Rounds

October 26: Dr. Michael B. Sporn, Professor of Pharmacology, Dartmouth Medical School, "Chemoprevention of Cancer: New Approaches, New Agents, New Mechanisms"

November 2: Dr. Andrei Kozlov, Director, St. Petersburg Biomedical Center, St. Petersburg, Russia, "Tumor Markers and Evolution"

CCR Grand Rounds are held 8:30 to 9:30 a.m. at the NIH campus in Bethesda, Md., in the Clinical Center's Lipsett Auditorium. ◆

Featured Meetings

This is a list of selected scientific meetings sponsored by NCI and other organizations. For locations and times and a more complete list of scientific meetings, including NCI's weekly seminars and presentations open to the public, see the NCI Calendar of Scientific Meetings at http://calendar.cancer.gov.

NCI Advisory Committee Upcoming Meetings

Date	Advisory Committee
Nov. 1	President's Cancer Panel
Nov. 4	NCI Director's Consumer Liaison Group
Nov. 8-9	NCI Board of Scientific Advisors

Selected Upcoming Meetings of Interest

Date	Meeting	NCI Speakers
Oct. 20-21	10th Annual Cancer Research Symposium	Dr. Andrew C. von Eschenbach, Director
Oct. 22-23	5th Asian American Cancer Control Academy	Dr. Andrew C. von Eschenbach, Director
Oct. 24-26	2004 Annual Joint Meeting of Association of American Cancer Institutes (AACI) & Cancer Center Administrators Forum (CCAF)	Dr. Karen H. Antman, Deputy Director, Translational and Clinical Sciences; Dr. Anna Barker, Deputy Director, Advanced Technologies and Strategic Partnerships
Oct. 29	2nd Annual Cancer Center Symposium at Baylor College of Medicine	Dr. Andrew C. von Eschenbach, Director
Nov. 4-6	Emerging Topics in Breast Cancer and the Environment Research	Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences

NCI Exhibits

NCI Exhibits are presented at various professional and society meetings. Further information about the NCI Exhibits program can be found at http://exhibits.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.

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