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Eliminating the Suffering and Death Due to Cancer

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Actual Cancer Deaths Decrease for Second Year Running

Marking what many cancer researchers are calling an important trend, the actual number of cancer deaths in the United States fell by more than 3,000 from 2003 to 2004, the most recent year for which mortality data are available. The steady decline in the rate of cancer deaths also continued.

The downturn from 556,902 deaths in 2003 to 553,888 in 2004 marks the biggest single-year decrease ever and the second consecutive year in which actual deaths—not just the death rate—have dipped.

"This decrease in actual number of cancer deaths, coupled with our SEER data showing a decline in the rate of cancer deaths since 1991, is extremely encouraging and highlights real progress," said NCI Director Dr. John E. Niederhuber.

The new mortality numbers were released as part of an annual report released by the American Cancer Society (ACS), *Cancer Statistics 2007*, which reports on the most recent mortality data, as well as providing

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Director's Update

Good News on Cancer Deaths Underscores Progress

During his visit to the NIH campus on January 17, President George Bush discussed cancer prevention with (left to right) HHS Secretary Michael Leavitt, NCI Director Dr. John E. Niederhuber, cancer survivor Dr. Grace Butler, and NIH Director Dr. Elias Zerhouni, among others.

Last week, the entire nation received the excellent news that, for the second year in a row—and for only the second time ever—the actual number of cancer deaths in the United States fell.

As a nation, our population is still growing and living longer, which makes this decline even more significant. It also further demonstrates the importance of closely tracking and studying incidence and death rates.

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cancer incidence and mortality estimates for the current year. Last year's publication showed a decrease of 369 cancer deaths from 2002 to 2003, the first-ever reported decline in cancer deaths since such statistics have been reported.

The new report has sparked intense optimism.

"This second consecutive drop in the number of actual cancer deaths, much steeper than the first, shows last year's drop was no fluke," said ACS Chief Executive Officer Dr. John R. Seffrin.

President Bush looks at kidney cancer cells during a tour of the laboratory of NCI's Dr. Marston Linehan on the NIH campus.

Even though the mortality rate has been decreasing for some time, added Dr. Gabriel N. Hortobagyi, president of the American Society of Clinical Oncology, the fact that the number of cancer deaths has decreased during a time of continued population growth "is very encouraging."

The drop in deaths was largely attributed to the reductions in smoking prevalence over the past several decades, improvements in cancer screening rates, and the use of increasingly effective treatment regimens. Screening's impact was most evident for colorectal cancer, which had the greatest reductions in cancer deaths among both men and women from 2003 to 2004.

According to Dr. Brenda Edwards, associate director of the NCI Surveillance Research Program, collaborative research is ongoing by the NCI-sponsored Cancer Intervention and Surveillance Modeling Network to better understand the impact of risk factor reduction and prevention, screening, and treatment on trends in death and incidence rates for cancers of the breast, colon-rectum, lung, and prostate.

The report, led by Dr. Ahmedin Jemal, from the ACS Department of Epidemiology and Surveillance Research, notes that cancer still accounted for about 23 percent of all U.S. deaths in 2004, with only heart disease responsible for more. Also, with the exception of a few cancer sites, Dr. Jemal and his ACS colleagues wrote, "[Cancer] incidence and death rates are consistently higher in African Americans than in Whites."

Although improvements in treatment for some cancers have lagged behind those seen in screening, Dr. Hortobagyi said he was optimistic that, with the pattern that's begun to develop with the newer targeted agents, that would start to change.

The pattern, he explained, begins with a "biological signal" in early-stage trials that a drug could be effective. It then moves into larger trials where it demonstrates some prolongation in disease progression and survival in previously treated metastatic disease. Finally, it transitions to testing in an early-stage disease with a curative intent.

"We've seen that with breast cancer and colorectal cancer, for example, and we're starting to see it in other tumors, as well," he said. ◆

By Carmen Phillips

More Data, Better Estimates

An important change to this year's ACS report, explained Dr. Linda Pickle, from NCI's Division of Cancer Control and Population Sciences (DCCPS), is that the estimates of cancer incidence for 2007 were based on data from far more cancer registries, using an improved prediction method.

Previous reports, she explained, included estimates that relied strictly on the original nine registries in NCI's Surveillance Epidemiology and End Results (SEER) program. That meant it only covered about 10 percent of the U.S. population. For the 2007 report, the estimates are based on data from SEER, CDC, and the North American Association of Central Cancer Registries. "Combined, those registries cover roughly 40 states and 86 percent of the U.S. population," she said. The new method also accounts for geographic variation of factors such as smoking patterns or income in producing incidence estimates. ◆

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Our investment in programs like SEER, for example, has allowed us to track the stabilization of cancer incidence rates and the overall decline in cancer death rates since the early 1990s. And through CISNET, NCI is supporting a consortium of researchers with expertise in modeling to help determine the relative contributions of various interventions to incidence and mortality rates. These important programs are greatly informing our efforts to lessen the cancer burden.

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Cancer Research Highlights

Gemcitabine Extends Disease-Free Survival in Pancreatic Cancer

Results from the largest randomized clinical trial of chemotherapy after surgery for pancreatic cancer, published in the January 17 *Journal of the American Medical Association*, show that the drug gemcitabine can increase disease-free survival without excessive side effects.

Investigators from Germany and Austria enrolled 354 eligible patients into the trial. All patients underwent complete resection of their pancreatic cancer. Following surgery, 179 patients received 6 cycles of chemotherapy with gemcitabine, each cycle consisting of 3 weekly injections followed by a 1-week rest period; 175 patients were assigned to an observation-only control group.

Dose modifications were allowed if patients experienced high-grade side effects. Investigators followed all patients with regular physical exams, blood tests, imaging, and quality-of-life assessments until death. The primary endpoint of the trial was disease-free survival, but investigators also measured toxicity and overall survival.

Sixty-two percent of patients in the gemcitabine group received all six cycles of scheduled chemotherapy, and 87 percent received at least one full cycle. High-grade side effects occurred infrequently and their incidence did not increase during the course of chemotherapy. Patients in the gemcitabine group experienced significantly longer median disease-free survival than patients in the control group (13.4 months vs. 6.9 months), without a decrease in quality of life.

Investigators observed a trend toward improved overall survival with the administration of gemcitabine, but this was not statistically significant. However, explained the authors, in light of their estimated survival analysis, "It seems highly likely that the difference in overall survival between groups will become statistically significant with a longer follow-up."

Review Reveals Common Flaws in Microarray Gene-Expression Studies

A detailed review of 42 cancer studies that used microarray technology to identify gene-expression profiles that can predict such things as therapeutic response or survival revealed common flaws in the studies' statistical analyses, according to a new report. Published in the January 17 *Journal of the National Cancer Institute (JNCI)*, the "critical review" of the 42 studies, all published in 2004, was conducted by Drs. Alain Dupuy, from the Hospital Saint-Louis in Paris, and Richard M. Simon, chief of NCI's Biometric Research Branch.

Although the volume of studies that use microarrays is increasing, the authors explained, questions have been raised about the validity of such studies' findings. The authors indicated that "microarray-based clinical investigations have generated both unrealistic hype and excessive skepticism."

Drs. Dupuy and Simon reviewed 90 studies published through the end of 2004 that related microarray-expression profiling to clinical outcome. They grouped the studies into three general categories: those that had an "outcome-related gene finding," which attempted to find specific genes expressed differently depending on patients' prognoses; those that focused on "class discovery" using statistical methods to group tumor specimens with similar gene-expression profiles; and those focused on "supervised prediction," which produce an algorithm that could predict clinical outcome on the basis of individual gene-expression profiles.

They then more closely reviewed 42 studies from this larger group published in 2004 and concluded that 50 percent contained at least one basic flaw. In 9 of the 23 outcome-related gene-finding studies, for example, there was "an unstated, unclear, or inadequate control for multiple testing." Other important flaws they found included overuse and/or inappropriate use of cluster analysis and reporting of biased estimates of prediction accuracy for supervised classifiers.

To help researchers avoid similar problems in future microarray data analyses, the paper includes guidelines for conducting these types of studies.

New Mechanisms Found for PTEN Protein

Tumor suppressor genes such as *PTEN* (phosphatase and tensin homolog) play a key role in controlling cell proliferation. Normal PTEN protein acts in a biochemical pathway that signals damaged cells to stop dividing and triggers them to self-destruct. Research teams from Memorial Sloan-Kettering Cancer Center and NCI's Center for Cancer Research (CCR) have uncovered ways that can-

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cer cells interfere with this suppressor action. Their findings, published in the January 12 *Cell*, could eventually yield new clinical strategies.

In one study, Dr. Xuejun Jiang and colleagues identified a key regulator of PTEN protein, a ubiquitin ligase known as NEDD4-1. In a mouse model, they found that NEDD4-1 was highly expressed in tumor cells and involved in posttranslationally modifying the PTEN protein by adding ubiquitin. Though the *PTEN* gene was not mutated, the ubiquinated PTEN protein was largely destroyed and its ability to suppress tumors was lost, thus qualifying *NEDD4-1* as a potential proto-oncogene.

In a second study, Dr. Pier Paolo Pandolfi and colleagues uncovered a novel role for the PTEN protein in the cell nucleus. In collaboration with Dr. Tom Misteli in CCR, they showed that normal PTEN protein is synthesized in the cytoplasm and modified by the NEDD4-1 ligase for entry into the nucleus, where it contributes to chromosome stability. A cancer mutation in the *PTEN* gene alters the protein, preventing it from entering the nucleus and acting as a tumor suppressor. "This is a beautiful example of basic research uncovering a novel cancer mechanism and pointing the way to entirely novel therapeutic strategies," said Dr. Misteli.

Calcium Offers Prolonged Protection From Colorectal Adenomas

Calcium supplements decrease the risk of colorectal adenomas 5 years after treatment ends, according to study results published in the January 17 *JNCI.*

Dr. John A. Baron of Dartmouth Medical School and colleagues followed participants of the Calcium Polyp Prevention Study, a double-blind, placebo-controlled, randomized trial of calcium supplements for subjects with a previous colorectal adenoma from 1988 to 1992. Researchers sent participants annual follow-up questionnaires that addressed medical events, including colonoscopies, as well as use of medication, vitamins, and dietary supplements. They obtained posttreatment information from 1999 to 2003 for 822 of the original 930 subjects.

Both the calcium treatment group and the placebo group had a similar number of colonoscopies, time to first and last colonoscopy, and use of calcium supplements after treatment ended. However, during the 5 years after treatment, those participants in the calcium treatment group had a significantly lower risk of all adenomas than those in the placebo group (31.5 percent vs. 43.2 percent).

The researchers wrote, "The persistence of the effect is a provocative finding, but one that is difficult to explain. It suggests that a 4-year course of calcium treatment alters the colorectal mucosa in such a way that it can resist the development of new adenomas that would otherwise become apparent several years later."

As for potential avenues of future research, Drs. Maria Elena Martinez and Elizabeth T. Jacobs of the Arizona Cancer Center wrote in an accompanying editorial that "individuals with lower rather than higher nutrient intakes are likely to benefit the most from supplementation and…those who have already exceeded the threshold of prevention may experience no added protection. Additionally, trials of adenoma recurrence should consider combinations of calcium and other agents." ◆

(Director's Update continued from page 2)
NCI had a tremendous opportunity last week to share the good news of the decline in deaths from cancer with President Bush. The President participated in a roundtable discussion on cancer and research with HHS Secretary Mike Leavitt, NIH Director Dr. Elias Zerhouni, National Human Genome Research Institute Director Dr. Francis Collins, and me. Two cancer survivors, Becky Fisher and Dr. Grace Butler, who is a member of the NCI Director's Consumer Liaison Group, also participated and both had powerful personal messages about their cancer experience that clearly touched the President.

It was the President's fifth visit to NIH and the first time that his focus was on the impact of cancer research achievements. At the roundtable, I had the opportunity to explain to President Bush some of the exciting genetics-related initiatives NCI is leading, including the Cancer Genetic Markers of Susceptibility and The Cancer Genome Atlas. As I told the President, programs such as these are laying the foundation for our ability to identify individuals at risk, develop prevention strategies, and design the next generation of cancer therapies. This new knowledge will greatly contribute to improvements in treatment and the continued reductions in cancer deaths.

Earlier in the day, President Bush toured the laboratory of Dr. Marston Linehan, chief of the Urologic Oncology Branch in NCI's Center for Cancer Research, and went to the clinical floor to visit with two of his patients. Over the past two decades, Dr. Linehan has used the power of genetics to pinpoint new molecular targets for therapy for kidney cancer, a disease that, until recently, has proven to be an intractable foe.

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Spotlight

Late in Life, Prostate Cancer Screening May Do More Harm than Good

The test used to screen for prostate cancer, the PSA (prostate-specific antigen) test, is controversial among many physicians. But even advocates of PSA testing do not recommend it for men who might not live long enough to see a benefit from screening.

The potential benefits of PSA testing are unclear, but experts agree that a man would probably have to live more than a decade to experience them. This is because the forms of prostate cancer that are detected by PSA testing late in life often progress slowly, as opposed to the more aggressive and often fatal forms of the disease that may occur earlier.

The potential harms of PSA testing, on the other hand, can occur immediately and are often substantial. These include additional testing, psychological distress, and side effects from treating a disease that might never have caused any harm.

For these reasons, most prostate cancer screening guidelines recommend against testing elderly men with limited life expectancy. But many men in their 70s and 80s are being screened anyway, and this has raised concerns among some physicians.

"This test can definitely cause more harm than benefit when used in an elderly population with multiple health conditions," says Dr. Louise Walter, a geriatrician and researcher at the San Francisco Veterans Affairs (VA) Medical Center and the University of California, San Francisco.

She led a recent survey of PSA testing in the VA medical system. Many physicians have been ordering PSA tests for men in their 70s and 80s, including some men in poor health, the researchers reported last November in the *Journal of the American Medical Association* (*JAMA*).

"I was surprised by how often very elderly men who have other severe diseases are getting prostate cancer screening," says Dr. Walter, who undertook the study after seeing some of her patients being harmed by PSA testing.

The test, she points out, measures blood levels of the PSA protein and is thought to be less informative in older men. Changes associated with aging such as a benign enlarged prostate can cause high PSA levels even when there is no prostate cancer.

And the benefits of testing remain unproven for all men, regardless of age or life expectancy. Two large randomized trials are investigating whether screening reduces prostate cancer deaths. Both have been ongoing for about 12 years and have yet to demonstrate a survival advantage for the men being screened.

Nonetheless, the prospect of having cancer based on the test is "very scary" to many men. "They may not realize that prostate cancer can range from an indolent disease that will never affect anyone to aggressive cancers that will kill them," says Dr. Walter.

Some of her patients became so distracted by looking for a disease they did not have that they neglected the diseases they did have.

She gives the example of an 85-year-old patient with inoperable heart disease. As she was treating him, another doctor tested his PSA and found it to be elevated. The patient grew anxious and requested a biopsy.

The result came back, and the doctor told him he had low-grade prostate cancer, which progresses slowly and kills relatively few people. The doctor told him not to worry, but the man couldn't stop worrying.

He considered himself a cancer patient and flew to Mexico for an alternative treatment. Meanwhile, his heart condition worsened, and he died of a heart attack 6 months later.

"He spent those final months worrying about his cancer, which was the least of his problems," says Dr. Walter. "He should never have been screened."

Her study last year suggests that his case may not be unique. More than half of nearly 600,000 men over age 70 had PSA testing at VA facilities in 2003. None of the men had a history of prostate cancer, and healthy men were screened at about the same rates as those with other diseases.

"This study points out that we are not doing a great job in terms of selecting people for screening," says Dr. Howard Parnes, who studies prostate cancer prevention in NCI's Division of Cancer Prevention.

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Physicians may not be taking the whole person's health picture into account when making this screening decision, he adds.

"It's not that old men shouldn't be screened, but we should be selective in screening because the benefits take a while but the harms are immediate," says Dr. Parnes.

The reasons for the high screening rates among veterans are not clear, but very few men asked for the test. Most likely, the tests were done as part of routine blood work that might include, for instance, testing cholesterol levels.

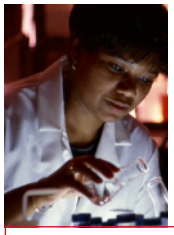
An editorial in the same issue of *JAMA* noted that physicians order the tests because patients overestimate their chances of dying from prostate cancer, as well as the efficacy of cancer treatment.

Another reason is that physicians are often rewarded for treating patients and may be severely penalized for missing a cancer.

"This dilemma is quite common in the current health care system and certainly requires urgent attention in the near future," wrote Dr. Peter Albertsen of the University of Connecticut Health Center in the *JAMA* editorial.

In the meantime, Dr. Walter hopes that more physicians will talk openly with their elderly patients about the potential harms of PSA testing. "This is really about not harming people by avoiding a procedure they don't need," she says. ◆

By Edward R. Winstead



Featured Clinical Trial

Sorafenib for Metastatic Prostate Cancer

Name of the Trial
Phase II Study of Sorafenib in Patients with Metastatic Androgen-Independent Prostate Cancer. See the protocol summary at http://www.cancer.gov/clinicaltrials/NCI-04-C-0262.

Principal Investigator
Dr. William Dahut, NCI CCR

Dr. William Dahut

Why This Trial Is Important

Prostate cancer cells often grow in response to hormones called androgens, which are naturally produced by the body. In most men with prostate cancer that has spread (metastasized), treatment to suppress these hormones is initially very effective in controlling cancer cell growth. However, over time, prostate cancer acquires the ability to grow without the help of hormones. This is called androgen-independent prostate cancer.

Many new drugs are currently being tested for the treatment of metastatic, androgen-independent prostate cancer. Sorafenib (Nexavar) is a type of anticancer drug that belongs to a class of drugs called small-molecule inhibitors. Small-molecule inhibitors block the activity of proteins in cancer cells that help promote cell division and survival.

Sorafenib inhibits the activity of at least three cancer-cell proteins involved in cell signaling—the transmission of information within a cell or between cells. The inhibition of multiple signaling proteins blocks both tumor-cell division and the growth of new blood vessels (angiogenesis) that feed the tumor.

"In the laboratory, sorafenib had activity against both signal transduction and angiogenesis in prostate cancer," explained Dr. Dahut. "We believe that angiogenesis is an important target in prostate cancer. Patients who have more vascular tumors at the time of initial diagnosis are more likely to eventually develop metastatic disease."

Who Can Join This Trial

Between 22 and 46 patients with metastatic prostate cancer that has progressed despite the use of hormone therapy will be enrolled in this trial. See the list of eligibility criteria at http://www.cancer.gov/clinicaltrials/NCI-04-C-0262.

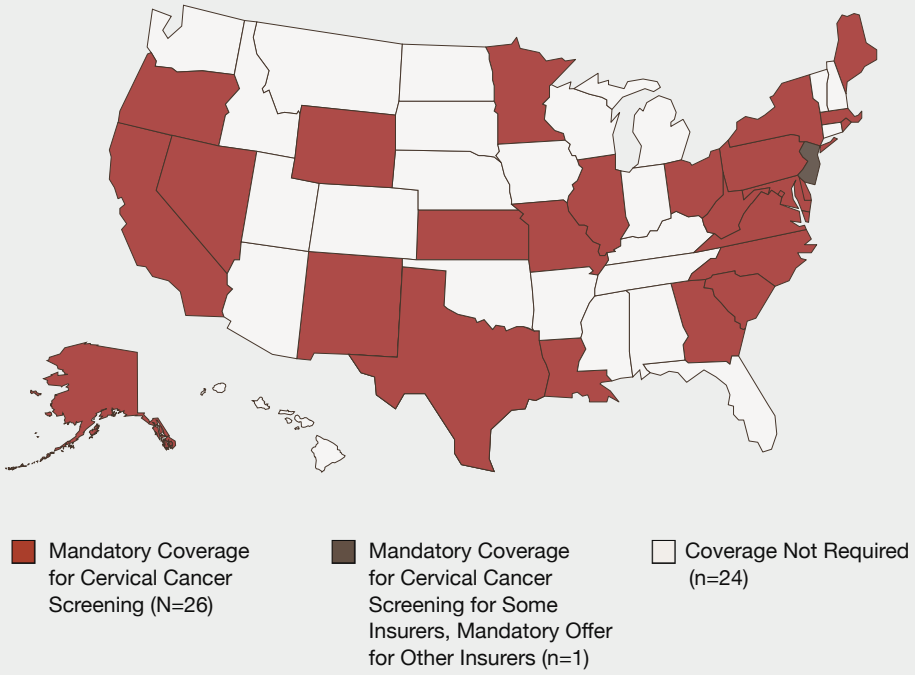
Study Site and Contact Information

The 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 toll-free call is completely confidential. ◆

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

Cervical Cancer Screening

States with Laws Requiring Third-Party Coverage for Cervical Cancer Screening* (as of September 30, 2006)



*(Applies only to HPV testing in Maryland)

January is Cervical Cancer Awareness Month. Pelvic exams, Pap tests, and tests for human papillomavirus (HPV) are essential for detecting cervical cancer or abnormalities that may lead to cervical cancer. The map shows the states with laws requiring third-party coverage for cervical cancer screening. For information on coverage of cancer screening in your state, go to http://www.scld-nci.net. For information on cervical cancer, go to http://www.cancer.gov/cancertopics/types/cervical. For information on HPV vaccines, go to http://www.cancer.gov/cancertopics/hpv-vaccines. ◆

CCR Grand Rounds

January 30: Dr. Charlotte Kuperwasser, Assistant Professor of Anatomy and Cellular Biology; Investigator, Molecular Oncology Research Institute, Tufts University-New England Medical Center. "The Use of Novel Zenograft Models to Study Stroma-Epithelial Interactions in Breast Cancer."

February 6: Dr. Glenn Merlino, Chief, Laboratory of Cancer Biology and Genetics, CCR, NCI. "Modeling the Genesis and Progression of Melanoma in the Mouse."

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 Amphitheater. ◆

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In addition to using genetics research to identify potential therapeutic targets, research into identifying a tumor's genetic makeup via gene-expression profiles is already beginning to influence decisions about patient care with existing therapies for breast cancer and lymphoma.

The advances being made in these and many other areas offer real hope for continuous progress. Even so, the new ACS report again confirms that minority and low-income populations shoulder a disproportionate cancer burden and aren't benefiting equally from these important advances. One way NCI is attempting to address this problem is by bringing the results of postgenomics science to patients where they live through the NCI Community Cancer Centers Program, with the hope of broadening access to clinical trials and to cutting-edge prevention, diagnosis, and treatment interventions.

With this new report, there is great cause for optimism, but an optimism that should be tempered by an understanding of the very real hurdles to progress we still face. These are challenges that we must address as a community. In doing so, such encouraging trends will become the rule, not the exception. ◆

Dr. John E. Niederhuber
Director, National Cancer Institute

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_012307/page8 ◆

A Conversation with…Dr. Grace L. Butler

Dr. Grace L. Butler is professor emeritus at the University of Houston. She is a colorectal cancer survivor who founded Hope Through Grace in 2002. Dr. Butler was recently appointed to serve on the NCI Director's Consumer Liaison Group (DCLG) and also participated in the roundtable discussion with President Bush during his recent visit to NIH.

The roundtable discussion included several topics about advances in cancer treatment and other issues. What aspects of the discussion were of particular interest to you?

I was very interested in Dr. Niederhuber's talk about NCI, the challenges they face, and his vision for the institute. I'm particularly interested in NCI's initiatives to create stronger alliances with community-based organizations. This is absolutely necessary as we seek to find better ways of putting research into practice, especially within lay communities and among those who may not participate in clinical trials or health education programs. I'm thinking especially of the underserved populations. Likewise, I had a great conversation with [NHGRI Director] Dr. [Francis] Collins about the importance of family health histories. Hope Through Grace emphasizes the importance of family health histories in our education programs.

What issues did the President seem particularly interested in and what were his comments or observations about those issues?

The President expressed very positive remarks about the agencies represented at the roundtable. He spoke of his commitment to NCI and of the increased levels of funding which have occurred under his Administration. In sum, the President was very receptive to what was being said around the table and the research that is being done. He urged each of us to use a vocabulary the average person could understand. I considered this to be an indication that he really wanted the public to benefit from the presentations and discussions at the table.

I sensed compassion from the President as I spoke about my journey and the nonprofit organization I've created. My involvement in the cancer community was the result of several meetings I had with health care providers about the issue of what is going to happen for uninsured people in our community. I especially remember asking a group of physicians about what was going to happen to those people: Are they simply going to be left to die? A gastroenterologist gave me a very cogent response and at the end he told me the answer to my question is "Yes."

When I heard that, I felt a lump in my throat. I couldn't believe this was happening in the United States. The information I gleaned from those meetings was the inspiration for founding Hope Through Grace. I recounted this story to the President. He expressed compassion for what I said and the issues I raised. He is also aware that, although the overall mortality rates for cancer are on the decline, there is a disproportionate incidence of cancer among some minority groups and we need to take assertive measures to eliminate these disparities. ◆

Featured Meetings and Events

A calendar of scientific meetings and events sponsored by the National Institutes of Health is available at http://calendar.nih.gov/app/MCalWelcome.aspx ◆

70 YEARS OF EXCELLENCE IN CANCER RESEARCH

If Memory Serves…

On August 5, 1937, President Franklin D. Roosevelt signed legislation that established NCI to support research related to the causes, diagnosis, and treatment of cancer.

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