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Division of Cancer Prevention

Featured Articles

11.01.05 | Fused Genes Found in Some Prostate Tumors

Researchers have identified several genes that are consistently merged, or fused, in some prostate tumors and could potentially be used to detect the disease. The discovery is the first example of gene rearrangements recurring in a solid tumor, although such changes are a hallmark of some blood cancers.

The findings, reported in the October 28 *Science*, suggest that prostate cancer is not a special case and that other common cancers such as lung, breast, and colon may involve recurrent gene rearrangements. The study was completed in less than 4 months, and the initial results surprised even the researchers themselves.

"We were surprised because these types of gene rearrangements have been associated with leukemia and lymphoma but not with solid tumors," says Dr. Arul Chinnaiyan of the University of Michigan Medical School, who led the study. "To find this change in a majority of prostate cancers suggests that it is important in the disease."

The researchers estimate that between 60 and 80 percent of prostate cancers have the rearrangement. They are developing techniques to detect the change in urine and blood.

When the rearrangement occurs, one of two cancer genes, *ETV1* or *ERG*, fuses with part of another gene, *TMPRSS2*. As a result of this fusion, the fused genes, which control other genes, become regulated by the hormone androgen and are at risk of stimulating too much genetic activity in the tumor cell.

"This is fantastic work," comments Dr. William Isaacs, professor of urology and oncology at Johns Hopkins University School of Medicine. "The results need to be independently replicated, but I have every reason to think this will happen rapidly."

The rearrangement may have gone undetected until now because solid tumors involve an overwhelming number of nonspecific, random aberrations.

To address this problem, two graduate students in Dr. Chinnaiyan's laboratory, Scott Tomlins and Daniel Rhodes, developed an algorithm that sifts through data on gene activity to find genes that are highly active in subsets of tumors.

Using the algorithm, called Cancer Outlier Profile Analysis, the team determined that *ETV1* and *ERG* were highly active in some prostate tumors.

Further study revealed that one but not both of these genes frequently fuses with *TMPRSS2* in prostate tumors. "This was a clue that the rearrangement played an important role in the development of prostate cancer," says Mr. Tomlins, noting that single fusion events typically cause some types of blood cancer.

Drugs could potentially be developed to inhibit the mutant genes, although this could take years. The drug imatinib (Gleevec), for instance, targets the gene fusion that causes chronic myelogenous leukemia.

"There are profound implications for diagnosis and treatment if it can be shown that this rearrangement occurs at the earliest stages of prostate cancer," says Dr. Sudhir Srivastava, chief of NCI's Cancer Biomarkers Research Program and director of the Early Detection Research Network, one of the NCI programs supporting the study.

The study does not demonstrate cause and effect, but "we know from other diseases that gene rearrangements are one of the major mechanisms in cancer," says Dr. Jacob Kagan, program director of NCI's Cancer Biomarkers Research Group. "We would now expect that there would be recurrent gene rearrangements in other common cancers as well." | *by Edward R. Winstead*

This story is available online at http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_110105/page2

11.15.05 | Updated Results Show Tamoxifen Continues to Prevent Breast Cancer

Updated results from the first-ever, large-scale breast cancer chemoprevention trial show that 5 years of tamoxifen (Nolvadex) decreases the risk of invasive and noninvasive breast cancer among women at increased risk, even after they've stopped taking the drug. According to the study authors, approximately 2.5 million women in the United States are at significant enough breast cancer risk that the potential benefit of prophylactic tamoxifen use significantly outweighs any potential risks.

The findings represent "a beginning from which a new paradigm for breast cancer prevention can evolve," says Dr. Bernard Fisher, principal investigator for the Breast Cancer Prevention Trial (BCPT). "Cohorts of women at increased risk for breast cancer, who could derive a net benefit from receiving tamoxifen, have been clearly defined."

The results may also dispel some perceptions about chemoprevention, says study co-author Dr. Leslie Ford, associate director of NCI's Division of Cancer Prevention.

"There is this notion that for cancer prevention, you have to take something for the rest of your life," she says. "In this study, the beneficial effects persisted beyond the last pill."

The results, published in the November 16 *Journal of the National Cancer Institute*, come from the 7-year follow-up data on more than 13,000 women who participated in the NCI-funded BCPT, a randomized, double-blind trial led by the National Surgical Adjuvant Breast and Bowel Project that compared 5 years of regular tamoxifen use with placebo in women at increased risk of breast cancer.

Consistent with the initial results, the updated data revealed that, overall, tamoxifen reduced the risk of invasive and noninvasive breast cancer (by 43 and 37 percent, respectively). The reduction was seen in all of the pre-identified trial subgroups, including those with a history of benign abnormalities such as atypical hyperplasia or lobular carcinoma *in situ*.

Although breast cancer risk was reduced across all age groups, a bright line of benefit versus risk of serious adverse side effects was seen

for participants 49 years of age and younger. For example, overall, there was a threefold increased risk of endometrial cancer, but there was only a slight and statistically insignificant increase in women under 49. A similar trend was seen for vascular side effects. There was also a reduced risk of fracture.

"That's one of the big messages from this trial—that tamoxifen is being underused in women under 50 who are at increased risk," says Dr. Ford. "For those women, there are demonstrable benefits with minimal risk of serious side effects."

The initial results from the BCPT, published in 1998, showed a nearly 50-percent reduction in invasive and 45-percent reduction in noninvasive cancers. The findings led to tamoxifen being the first chemopreventive drug approved by the Food and Drug Administration (FDA).

But in the study, tamoxifen use also was associated with an increased risk of serious side effects, including endometrial cancer, pulmonary embolism, and deep-vein thrombosis.

The 7-year follow-up data, with an average follow-up of 74 months, suggest those risks continue. However, because the trial was unblinded after the initial results were released, it also may have introduced some bias into the side effects data, Dr. Ford notes, because women who found out they were on tamoxifen were more likely to pursue follow-up related to real or perceived symptoms of side effects.

Dr. Susan M. Domchek, an assistant professor of medicine at the Abramson Cancer Center of the University of Pennsylvania, says she often offers tamoxifen to appropriate patients, but "many decline to take it in this setting." So although educating clinicians about tamoxifen's benefits is still needed, "one of the major problems...is the reluctance of patients to take it," she says. "We can work on the first part more easily at this point than we can on the second." | *by Carmen Phillips*

This story is available online at http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_111505/page2

1.4.05 | NIH Halts Use of COX-2 Inhibitor in Large Cancer Prevention Trial

On December 17, 2004, the National Institutes of Health (NIH) announced that it suspended the use of the COX-2 inhibitor celecoxib (Celebrex) for all participants in a large colorectal cancer prevention clinical trial conducted by the National Cancer Institute (NCI). The study—the Adenoma Prevention with Celecoxib (APC) trial—was stopped because analysis by an independent Data Safety and Monitoring Board showed a 2.5-fold increased risk of major fatal and nonfatal cardiovascular events for participants taking the drug compared with those on a placebo.

Additional cardiovascular expertise was added to the safety monitoring committee at the request of the steering committee for this trial after a September 2004 report that the COX-2 inhibitor rofecoxib (Vioxx) caused a two-fold increased risk of cardiovascular toxicities in a trial to prevent adenomas. The APC trial is a study of more than 2,000 people who have had a precancerous growth (adenomatous polyp) removed. They were randomized to take either 200 mg of celecoxib twice a day, 400 mg of celecoxib twice a day, or a placebo for 3 years. The trial began in early 2000 and is scheduled to be completed by spring 2005.

Investigators at the 100 sites in the APC trial located primarily in the United States, with a few sites in the United Kingdom, Australia, and Canada, have been instructed to immediately suspend study drug use for all participants in the

trial, although the participants will remain under observation for the planned remainder of the study.

"Data from the report on rofecoxib informed us of the need to focus on specific cardiovascular issues, and our institutes brought in the experts to do so," said NIH Director Dr. Elias A. Zerhouni. "Our overwhelming commitment is to advance the health and to protect the safety of participants in clinical trials. We are examining the use of these agents in all NIH-sponsored clinical studies. In addition, we are working closely with our colleagues at FDA to ensure that the public has the information they need to make informed decisions about the use of this class of drug."

"The rigor of our clinical trials system has allowed us to find this problem," said NCI Director Dr. Andrew C. von Eschenbach. "We have a strong system that provides us with the opportunity to both find ways to effectively treat and prevent disease and to do so in a way that protects the lives and safety of the participants."

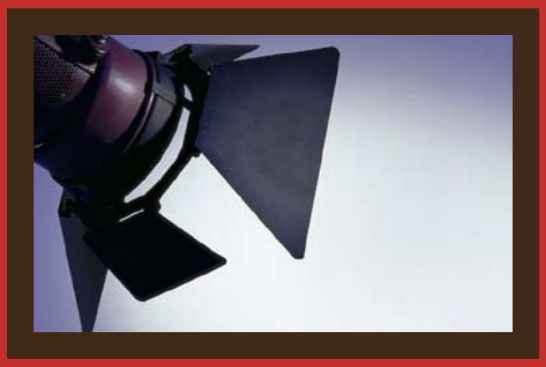
NIH sponsors more than 40 studies using celecoxib for the prevention and treatment of cancer, dementia, and other diseases. In light of these new findings, Dr. Zerhouni requested:

- A full review of all NIH-supported studies involving this class of drug
- That all NIH institutes inform the principal investigators for all of these studies, asking the PIs, in turn, to communicate directly with their study participants and explain the risks and benefits
- That NIH asks each investigator to inform NIH of their plan to analyze their data in light of the information
- That the Institutional Review Boards for all related trials assess the new information and conduct a safety review

Questions and answers about the APC trial are available at http://www.nih.gov/news/pr/dec2004/od-17Q&A.htm. More information about regulation of COX-2 inhibitors is available from the FDA at http://www.fda.gov/cder/drug/default.htm. | *By Jo-Ann Kriebel*

Division of Cancer Prevention

Special Report and Spotlights



9.27.05 | Blood Test Reveals Protein "Signature" for Prostate Cancer

Researchers studying the body's response to prostate cancer have developed a blood test for diagnosing the disease, and preliminary experiments suggest that it may be more reliable than the standard diagnostic blood test, the prostate-specific antigen (PSA) test.

The PSA test measures the blood levels of a single enzyme that is elevated in some men with the disease. But the levels can be elevated for reasons other than cancer, resulting in many biopsies that ultimately do not diagnose cancer.

The new test detects 22 proteins made by the immune system to fight the cancer. In a comparison, testing for the proteins was more accurate than PSA testing to correctly identify blood from prostate cancer patients while not misidentifying blood from a group of controls, according to findings in the September 22 *New England Journal of Medicine*.

"We view this study as a demonstration that screening blood for proteins produced in response to prostate cancer is a potential strategy for detecting the disease," says Dr. Arul Chinnaiyan of the University of Michigan Medical School in Ann Arbor, who led the study.

His team analyzed blood samples from 331 prostate cancer patients in the early stages of disease, and from 159 men with no history of cancer. Using a combination of technologies, they identified a "protein signature" for the disease.

The signature consists of 22 antitumor proteins known as "autoantibodies." All tumors produce abnormal proteins that are recognized by the immune system as foreign; the body responds by producing autoantibodies against them.

"Our strategy was to take advantage of the body's own immune system, which fights things that are foreign, like bacteria and viruses and cancer," says Dr. Chinnaiyan. The test is experimental and the results need to be validated, he adds.

Similar approaches have been used in other cancers to study individual autoantibodies. Last year, Dr. Chinnaiyan and his colleagues reported that some prostate cancer patients make autoantibodies against an enzyme called α-methylacyl-CoA racemase.

The new study defines a more representative collection, or panel, of autoantibodies, though the panel is a continual work in progress, notes Dr. Chinnaiyan. Efforts to define the autoantibodies for a given cancer characterize the emerging field of cancer immunomics.

A clinically validated panel, the researchers suggest, might be used in conjunction with PSA testing to help determine which patients truly need a biopsy to rule out a cancer diagnosis. The test could be given to patients who receive a positive PSA test but have not yet had a biopsy.

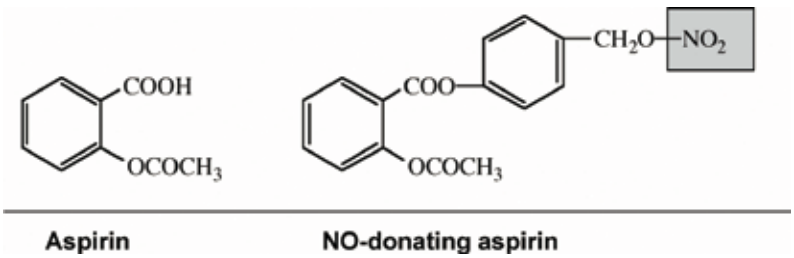
"We are cautiously optimistic, but there's a tendency to sensationalize results from early studies like this one," says Dr. James Montie, chairman of the Department of Urology at Michigan and a member of the research team.

He and others would certainly welcome a diagnostic test that is less vulnerable than the PSA test to confounding factors such as benign enlargement of the prostate.

Dr. Sudhir Srivastava, chief of NCI's Cancer Biomarkers Research Program and director of the Early Detection Research Network, which supported the study, is also optimistic. "I'm hopeful the results will be validated because the research was done so elegantly in terms of technology," he says.

"This is all part of continuing efforts to learn what goes wrong during prostate cancer and to identify biomarkers," says Dr. Srivastava. "The novelty comes from using the body's defense system to detect cancer rather than looking at, say, genetic mutations." | *By Edward R. Winstead*

fig. 1 | The chemical structure of standard aspirin compared to the structure of nitric oxide (NO)–donating aspirin. NO–donating aspirin is being tested as a chemopreventive agent against colorectal cancer.



4.5.05 | Aspirin Offers Promise for Colorectal Cancer Prevention

Most people probably would not associate car exhaust fumes with cancer prevention. Those fumes, however, contain nitric oxide (NO), gas molecules also produced by human cells that are essential to the regulation of a host of important biological functions, from the immune response to blood pressure.

A great deal of research these days is focused on taking advantage of some of this air pollutant's remarkable regulatory talents. Human clinical trials are now testing, for example, "NO-donating" compounds to treat diseases and conditions as diverse as asthma and Alzheimer's. Last week the first human clinical trial was initiated testing an NO-donating aspirin as a chemopreventive agent against colorectal cancer.

The research into this compound, a derivative of aspirin-releasing nitric oxide dubbed NCX4016, builds on data from epidemiologic studies and clinical trials showing that regular use of traditional aspirin can significantly reduce colon polyp formation in those at high risk of developing them, including those already treated for colorectal cancer. According to Dr. Basil Rigas, chief of the Division of Cancer Prevention at the State University of New York at Stony Brook, in laboratory and animal model studies he has led, NCX4016 has proven hundreds of times more potent than traditional aspirin in inhibiting growth of colon cancer cells in cell cultures. And in a mouse model of colon cancer, mice given NCX4016 daily for

3 weeks had a 59 percent tumor reduction on average. In a similar study using rats, tumor growth was reduced by 75 percent, and new tumors failed to grow. In both cases, the drug was effectively free from toxicity.

The gastrointestinal (GI) toxicity often seen with regular aspirin use and other nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen fueled the development of NO-donating NSAIDs in the mid-1990s. "NO," says Dr. James Crowell, a program director in the NCI Division of Cancer Prevention, "stimulates vasodilation and mucous secretion by the cells that line the GI tract." So an NSAID that releases NO may effectively nullify the NSAID's ability to cause serious, sometimes life-threatening problems such as bleeding ulcers.

What initially brought NO to the research forefront, however, was something altogether different: the discovery in the late 1980s of its role as a signaling molecule in the cardiovascular system—the first time a gas molecule was found to participate in the communication network within cells that regulate functions such as growth, division, and death. The discovery, for which a trio of scientists was awarded the 1998 Nobel Prize, spurred researchers from across the globe to see if NO played a similar role in other organ systems.

What they found is that "nitric oxide regulates nearly every tissue in your body," says Dr. David Wink, a principal investigator in NCI's Center for Cancer Research Radiation Biology Branch who has been studying the ubiquitous molecule for nearly 15 years. His lab's work has led to some intriguing discoveries. "We have found that changes in the doses of our NO donor compounds by very small amounts cause profound changes in tumor cells and signal transduction," Dr. Wink says.

Following on their studies showing that, in cell culture, tumors can use NO to promote angiogenesis, Dr. Wink's laboratory is now in the early stages of investigating how inhibiting NO affects standard cancer therapy. "We've found that if we inhibit NO after radiation or chemotherapy treatments, we see tremendous increases in the treatments' efficacy," he says.

As for chemoprevention, NCX4016's promise, Dr. Rigas notes, is not limited to colorectal cancer. In an animal model system of pancreatic cancer, treatment or pre-treatment with NCX4016 prevented 90 percent of pancreatic cancers. His laboratory has received several grants to study NO's mechanism of action, work primarily focused on elucidating what intracellular signaling pathways it affects. So far, several pathways have stood out, including NF-ÐB and Wnt, both of which are thought to be involved in carcinogenesis.

The molecular biology of NO in cancer is still not well understood, stresses Dr. Crowell. Additional research will provide insight into the potential long-term impact of NCX4016's use and help guide its potential use in combination with other therapies.

The trial initiated last week—supported by NCI and conducted in conjunction with NicOx, the French company that is developing a number of NO-donating agents for a wide variety of indications—will include a pharmacokinetic component aimed at answering some of those questions. It will recruit 240 patients at high risk of colorectal cancer and test whether, after 6 months of treatment, the drug can prevent or arrest the growth of microscopic lesions found in the colon lining, called aberrant crypt foci, which are thought to be polyp precursors.

Although the potency NCX4016 has displayed in laboratory and animal model studies is enticing, says Dr. Rigas, in the relatively new area of chemoprevention, establishing safety is paramount. "With chemoprevention, you're administering an agent to an otherwise healthy individual at risk for developing a cancer," he says. "And that person is committed to receiving that agent for a very long time." | *By Carmen Phillips*

10.11.05 | Rinse and Spit: Saliva as a Cancer Biomarker Source

It's home to more than 700 types of bacteria (by current estimates, at least), can be a source of infection, but also has wound-healing properties. It's essential for swallowing and digestion, but, in many cultures, to expel it at somebody is the ultimate insult. And now this slimy body fluid—saliva—is gaining a reputation in biomedical research circles as an effective source for detecting the hidden presence of disease, including some types of cancer.

Most research into cancer biomarkers has focused on blood components, such as plasma or serum. Saliva, on the other hand, has been largely overlooked as a source of biomarkers. It has long been considered a hostile environment, riddled with bacteria and other detritus that would yield adulterated samples incapable of generating reliable and reproducible results.

But that perception is beginning to change. According to Dr. Sudhir Srivastava, director of NCI's Early Detection Research Network (EDRN), which focuses on identifying and validating novel biomarkers, recent data on saliva-based biomarkers—although preliminary—are promising.

"And, saliva-based technology is desirable," he says, "because it's a noninvasive means of detecting biomarkers."

Head and neck cancers have been the focus of most saliva-based biomarker research. These cancers typically are detected during clinical examinations, but often not until they have already progressed to late-stage disease—a big reason why 5-year survival rates have been mired in the 50 percent range for several decades.

Detecting these cancers at earlier stages, with the aid, for instance, of a saliva-based diagnostic test, could increase 5-year survival to 80 to 90 percent, according to Dr. Elizabeth Franzmann, of the Department of Otolaryngology at the University of Miami. This could help avoid some of the morbidity associated with treatment, including disfigurement and significant swallowing difficulties.

Public attention to saliva-based biomarker research received a significant boost last December with the publication of a pilot study conducted in the lab of Dr. David Wong, of the UCLA Jonsson Comprehensive Cancer Research Center. Elevated levels of seven different RNAs, they reported, could distinguish patients with oral squamous cell carcinoma (OSCC) from controls with 91 percent sensitivity and specificity.

Dr. Wong says that his lab has now performed 4 independent detection trials with 272 subjects and controls.

"These seven markers behave consistently throughout these trials, showing that they are significantly elevated in individuals with oral cancer compared to age- and gender-matched controls," he explains. "It really is quite an amazing observation."

Saliva-based detection methods don't have to be limited to head and neck cancers, Dr. Wong argues. As-yet-unpublished studies by his lab using the same RNA approach to detect early-stage breast cancer, he says, "have been very promising."

Dr. Wong's lab is working with newer testing technologies developed with funding from the National Institute of Dental and Craniofacial Research, which is investing significantly in this area. But other researchers are trying to tease out diagnostic clues from saliva using more conventional assays and are finding success.

Dr. Franzmann led a small study published earlier this year in which she used the conventional ELISA test to detect elevated levels of a soluble form of the protein CD44 (solCD44), which was found to reliably identify patients

with head and neck squamous cell carcinoma (HNSCC), regardless of the tumor stage. The closer the cancer to the main oral cavity, the more sensitive the solCD44 levels.

"We've even had cancers where no tumor can be seen in the upper aerodigestive tract, but there is a metastasis to the lymph node," she says. "So that's telling us that it may be capable of picking up disease that we can't even see."

Like Dr. Wong's group, other researchers are also looking at more atypical markers. Dr. Joseph Califano of the Department of Otolaryngology-Head & Neck Surgery at Johns Hopkins Medical Institutions and colleagues recently reported that increased levels of mitochondrial DNA (mtDNA) in saliva also strongly correlated with HNSCC, particularly late-stage disease.

Based on this study and other work, Dr. Califano believes mtDNA has the potential to be most valuable as a surveillance tool in patients who have already been treated for HNSCC.

Research into saliva-based diagnostics definitely has a way to go, though, Dr. Califano stresses.

"Specificity is the real challenge. For screening, whether it's for modestly rare diseases or common diseases of any type, if you don't have high specificity, your false-positive rate becomes quickly, unacceptably very high," he says.

Most of the saliva studies to date, cautions Dr. Srivastava, have been pilots. The research is now at the point where, if it is to enter the clinical realm, "It needs to undergo rigorous validation studies," he says. "That means taking a broad spectrum of cases and controls and then seeing whether the markers consistently distinguish between the two."

EDRN is talking with Dr. Wong about the possibility of a national validation trial of his lab's RNA panel/assay for OSCC.

| *By Carmen Phillips*

Division of Cancer Prevention

Focus on the Community Clinical Oncology Program

9.13.05 | For More Than 20 Years, CCOPs Define Commitment, Success

There are many examples of successful National Cancer Institute (NCI) programs that span every part of our research enterprise. With this special issue of the *NCI Cancer Bulletin*, we are honoring a program that has come to represent the very definition of success: the Community Clinical Oncology Program (CCOP).

In 1982, a Request for Applications was issued soliciting participants for a unique program that would bring together community hospitals, the growing cadre of community oncologists, and other local health care providers into a nationwide network for conducting cancer clinical trials. Who could have imagined just how effective this program would become? But here we are, more than 20 years later, with CCOPs having enrolled more than 172,000 patients into cancer treatment and prevention trials.

From the beginning, there were those who doubted the program would work, who believed community providers could not stand up to the rigors of conducting large clinical trials. But time and again, these critics have been proven wrong. Analysis of CCOPs' performance over the years has consistently shown that they are not only skilled at recruiting patients, but also produce quality data and ensure the adoption of new standards of care by community providers.

The CCOPs' role in treatment trials has been critical. But under the inspired, excellent leadership of Dr. Peter Greenwald and his staff in the Division of Cancer Prevention (DCP)—including the program's current head, Dr. Lori Minasian, and its previous leader of 10 years, Dr. Leslie Ford—the cancer prevention and control arena is where the CCOPs have helped stake new ground. Indeed, the first drug ever approved for cancer prevention, tamoxifen, might never have been if the CCOP network had not conducted the Breast Cancer Prevention Trial, on which the approval was based.

From the beginning, the individuals and institutions participating in the CCOP network have had a remarkable commitment to its success. That commitment can be seen in the unselfish and cooperative manner in which they work with the NCI Cooperative Group and Cancer Centers, collectively known as the Research Bases. During a time when we are still working to more effectively integrate team science into cancer research, the CCOPs' collaboration with the Research Bases has been the epitome of teamwork.

A perhaps underappreciated component of the CCOPs is their participation in symptom management trials. These trials may not garner as many headlines as treatment and prevention trials, but their importance in developing interventions to reduce side effects such as nausea and mucositis is undeniable.

Finally, there is no greater indicator of success than imitation, which is why two institutes at the National Institutes of Health (NIH) have followed the CCOP model in developing community-based clinical trial networks to test new treatments for HIV and drug abuse.

In many respects, the success of the CCOPs is not a surprise. The genesis of the term "cancer community" is rooted in the unwavering commitment displayed by so many individuals in this country to defeating this disease. So it should come as no shock that, more than 20 years ago, when NCI reached out to communities to play a new role in advancing cancer research, they exceeded every expectation—and continue to do so. | *by Dr. Andrew C. von Eschenbach, Director, National Cancer Institute*

9.13.05 | Minorities Gaining Access to Clinical Trials

This past June, when the NCI Clinical Trials Working Group focused on the ongoing need to increase recruitment of minority populations to cancer clinical trials, a key element of their proposed solution was to fund more Minority-Based Community Clinical Oncology Programs (MB-CCOPs), and for good reason. Over the last decade, more than 5,500 minorities have enrolled in both treatment and prevention clinical trials sponsored by NCI through the MB-CCOP network.

fig. 2 | **Dr. Worta McCaskill-Stevens, MB-CCOP Program Director**

The MB-CCOPs were launched in 1990 as part of the efforts of the CCOPs to deliver the best cancer care to patients, wherever they live. At least 40 percent of the local populations served by MB-CCOPs are minorities and the programs have had a disproportionately positive effect: In 2003, for instance, the MB-CCOPs accounted for less than 20 percent of the CCOP network but enrolled half of the minority patients in the studies. (See August 2 *NCI Cancer Bulletin* and August 2 *Journal of Clinical Oncology*.)

"Despite the recruitment challenges remaining, and any new barriers that may arise, the MB-CCOPs have shown that they can use their infrastructure to engage community health care providers and successfully recruit minorities into prevention trials," says Dr. Worta McCaskill-Stevens, the MB-CCOP program director in NCI's DCP.

Minority communities experience an unequal burden of cancer, and the professionals who work with them face challenges in

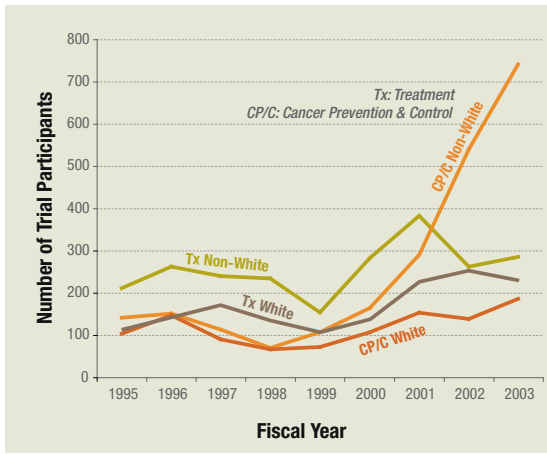


fig. 3 | **MBCCOP Accruals to Cancer Treatment and Cancer Prevention and Control Clinical Trials by Race, FY 1985-2003**

recruiting for trials. In some African American communities, for example, earning the trust of patients and their families is essential.

"We address the issue of trust immediately, and we focus on educating people about the clinical trials that are available," says Dr. Lucile Adams-Campbell of the Howard University Cancer Center in Washington, D.C., who directs the District's MB-CCOP.

MB-CCOPs also benefit the communities they serve. In Puerto Rico, for example, the program targets cancer patients who cannot afford the drugs and treatments being evaluated. This was the case in trials that recently led to the new standard of care for HER-2 positive breast cancer. "This program offers patients hope and state-of-the-art therapies in their own communities from people who know their language and their culture," says the director, Dr. Luis Baez of the University of San Juan.

Dr. McCaskill-Stevens feels that MB-CCOPs also are in a unique position to address issues critical to minority populations and cancer, including mentoring investigators, sharing recruitment strategies with other institutions,

identifying trends in cancer incidence in their local communities, and contributing to trial designs that account for competing minority health issues.

Dr. McCaskill-Stevens is optimistic about the increasing access that minorities will have to cancer trials, whether for prevention or treatment. "The future of minority participation in cancer trials rests with the burgeoning potential of this network," she says. "Their early successes will continue to bring quality health care delivery to diverse groups for years to come." | *by Edward R. Winstead*

This story is available online at http://www.cancer.gov/ncicancerbulletin/NCI/Cancer_Bulletin_091305/page3

9.13.05 | A Conversation with Lori Minasian

Dr. Minasian has been chief of the Community Oncology and Prevention Trials Research Group, which administers the CCOPs, since 1997.

What do you think are the CCOPs' most important contributions to cancer research and prevention?

The first major accomplishment is that we've proven community physicians can be significant contributors (in terms of both quality and quantity) to clinical trials that set the national standards for quality care in cancer. Next, CCOPs have shown that cancer prevention and cancer control trials can be done in the community setting. And finally, the results of the landmark prevention trials themselves are a major contribution—the proof of principle that an agent can reduce a person's risk for developing cancer.

Why are the CCOPs so successful at recruiting patients?

The program succeeds because CCOP physicians and their staffs are motivated to succeed. They believe that clinical trials allow them to offer state-of-the-art care for cancer patients and people at risk for cancer. These trials are carried out in the community setting, not as an exception to everyday care, but rather as part of excellent delivery of cancer care. The program lets stable resources get into the hands of the community physicians who have demonstrated their ability to accrue to clinical trials and provides them with significant, ongoing support so they can continue to do so.

fig. 4 | Dr. Lori Minasian, Chief of the Community Oncology and Prevention Trials Research Group

CCOP physicians receive training and support from NCI. What have the CCOPs taught NCI about community oncology?

These physicians, nurses, and support staff are incredibly committed to their patients, as well as to clinical trials. They have taught me that community physicians can integrate clinical research into their very busy practices when they have sufficient resources.

This story is available online at http://www.cancer.gov/ncicancerbulletin/NCI/Cancer_Bulletin_091305/page2

Moments in Community Clinical Oncology Program History

July 1982 – NCI launches the Community Clinical Oncology Program (CCOP) to establish a cancer control effort combining the expertise of community oncologists with NCI clinical research programs, and brings the advantages of clinical research to cancer patients in their communities.

September 1983 – The original 63 CCOPs, located in 34 states, are funded.

1987 – First evaluation of CCOP finds the program effective in enrolling patients in clinical trials and getting physicians to adopt trial results as standards of care.

1989 – Minority-Based CCOPs are established to focus on access to minority populations. Universities, as the primary health care providers for minorities, are permitted to apply to the program.

April 1998 – BCPT results are announced: Women taking tamoxifen had 45 percent fewer breast cancer diagnoses than women on the placebo, proving that breast cancer can be prevented.

October 1993 – The Prostate Cancer Prevention Trial (PCPT) begins. PCPT evaluates finasteride as a prostate cancer prevention drug, and is coordinated by the Southwest Oncology Group.

June 1993 – The Colorectal Adenoma Prevention Study (CAPS) is begun under the direction of the Cancer and Leukemia Group B, using the CCOP network. The trial evaluates whether aspirin will reduce the development of adenomas in people who have already had early-stage colorectal cancer.

April 1992 – The CCOP network is used for the first time to conduct a large prevention trial to evaluate the efficacy of tamoxifen to prevent breast cancer in women at increased risk of the disease. The National Surgical Adjuvant Breast and Bowel Project coordinates the Breast Cancer Prevention Trial (BCPT).

1998 – An Institute of Medicine report recommends that the National Institute on Drug Abuse and the Center for Substance Abuse Treatment use the NCI CCOP model to conduct community-based trials of drug and alcohol treatments.

May 2002 – CAPS results are presented at the American Society of Clinical Oncology meeting: Daily aspirin use reduced the development of adenomas by 35 percent in patients with previous colorectal cancers.

June 2003 – PCPT results are released: Men taking finasteride had 25 percent fewer prostate cancer diagnoses than men on the placebo, proving that prostate cancer can be prevented.

2005 – NCI funds 50 CCOPs across 30 states;13 MB-CCOPs in 10 states, Puerto Rico, and Washington, D.C.; and 14 Research Bases.

Community Clinical Oncology Programs (CCOPs)

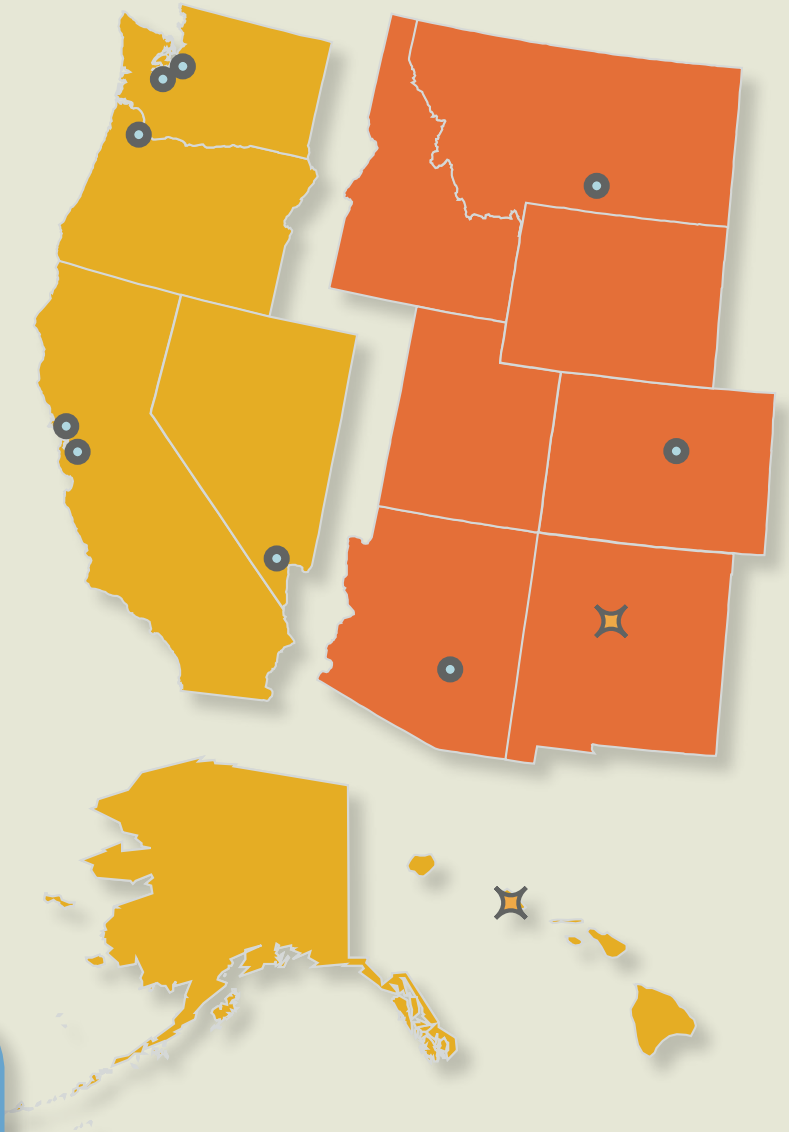
There are 415 hospitals participating in the CCOPs, ranging from 1 to 23 per program.

There are 3,675 physicians in the CCOPs, ranging from 2 to 132 per program.

There are 68 active prevention and control trials and 283 active treatment trials in the CCOPs network.

The Study of Tamoxifen and Raloxifene (STAR), one of the largest breast cancer prevention studies ever conducted, completed recruitment in October 2004 with 19,747 women, 6,579 at CCOP sites (33 percent). The Southeast Cancer Control Consortium CCOP was the top accruer to STAR.

Although Minority-Based CCOPs make up less than 20 percent of CCOP grantees, they contribute 33 percent of the network's minority accruals and 7 percent of minority patients on all cooperative group trials.



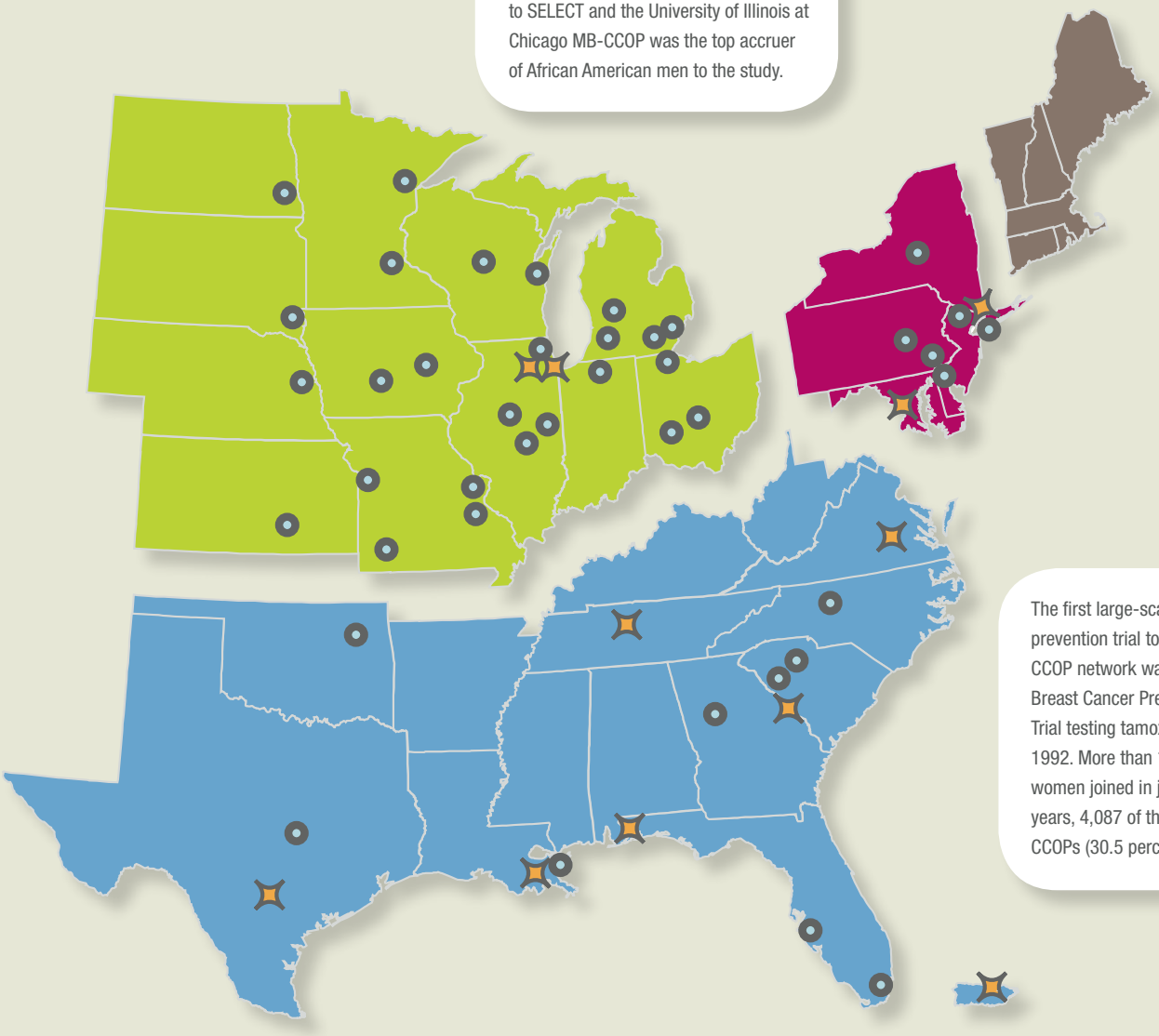
The most common symptoms addressed in CCOP symptom-management trials are pain, anorexia, mucositis, neuropathy, and hot flashes.

The primary NCI mechanism for conducting phase III clinical trials in symptom management, palliative care, and other cancer control issues is the CCOP network.

Since 1982, CCOPs have enrolled 104,160 patients—approximately 1/3 of all NCI treatment trial participants—to NCI-sponsored treatment clinical trials.

The Selenium and Vitamin E Cancer Prevention Trial (SELECT), an ongoing study of dietary supplements in prostate cancer prevention, enrolled 35,534 men in 3 years; 10,270 (29 percent) of these at CCOP sites. The Upstate Carolina CCOP was the second top accruer overall to SELECT and the University of Illinois at Chicago MB-CCOP was the top accruer of African American men to the study.

Since 1990, prevention clinical trials conducted by the CCOP program have enrolled 92,300 people at risk for cancer.



The first large-scale prevention trial to use the CCOP network was the Breast Cancer Prevention Trial testing tamoxifen in 1992. More than 13,388 women joined in just 4 years, 4,087 of them at CCOPs (30.5 percent).

One of the first clinical trials to show cancer- preventive effects of aspirin was the CCOP-conducted Colorectal Adenoma Prevention Study in 2003, after several epidemiologic studies linked such non-steroidal anti-inflammatory drugs to lower rates of colorectal adenomas (polyps).

The CCOP-conducted Prostate Cancer Prevention Trial (PCPT) enrolled 18,882 participants—7,312 from CCOP sites (38.7 percent). The drug studied, finasteride, is the first drug found to reduce the risk of prostate cancer.

Tamoxifen, which in 1998 was the first drug approved by the FDA for cancer risk reduction, was approved based on the results of the CCOP-conducted Breast Cancer Prevention Trial.

9.13.05 | Why CCOP Physicians Participate in Prevention

fig. 5 | Dr. James L. Wade III

By Dr. James L. Wade III, Principal Investigator, Central Illinois CCOP, Decatur, Illinois

CCOPs initially arose as mechanisms that would enable community oncologists to participate in cooperative groups' cancer treatment studies. Often such protocols would include the investigation of a new drug. Some studies would redefine the standard of care for a particular disease.

Although these programs focused on treatment trials have been quite successful, community oncologists have come to recognize that the greatest reduction in the cancer burden will only come from disease prevention. All of the advances in prolonging survival and reducing relapse pale in comparison to cancer prevention. CCOP investigators have learned this from their patients, their patients' families, and their communities. CCOPs now view themselves as the best medium for chemoprevention studies at the local level.

Indeed, CCOPs are the ideal platform for such prevention studies because they align the principal investigator's recognition that chemoprevention holds great promise with his or her local community's desire to participate in the research process..

The successes of such cancer awareness events as the "Race for the Cure" and the "Walk for Life" are clues to how important local communities feel about doing their part to help. CCOPs then take this local interest and desire to participate to a higher level by enrolling at-risk individuals into studies designed to reduce cancer incidence.

The cooperative groups have a responsibility to harness their considerable expertise to design a national prevention program for all malignancies that are candidates for prevention strategies. When armed with good national large-scale prevention programs, the CCOPs can fulfill their initial promise of truly reducing the cancer burden.

9.13.05 | Why I Am a CCOP Physician

fig. 6 | Dr. Richard L. Deming

By Dr. Richard L. Deming, Medical Director, Mercy Therapeutic Radiology Associates, Des Moines, Iowa

Cancer treatment is an evolving process. The knowledge we gain from the results of clinical trials ultimately determines what the standard treatment for a particular type and stage of cancer will be.

During our residencies at academic medical centers we learned the value of evidence-based medicine. We studied the landmark clinical trials that influenced our current recommendations and we participated in new trials destined to influence future standards.

When we completed our residencies, we chose whether to stay in the academic world or to join the ranks of community physicians. Many of us struggled with this decision because we enjoyed the stimulation of the university setting, and felt the good that comes from working to advance the treatment.

Those of us who go into private practice don't give up our intellectual curiosity or our desire to help advance the knowledge of cancer treatment. Participation in clinical trials through the CCOPs allows us to continue contributing to our profession and helping to improve the quality of patient care.

For me, participation in the North Central Cancer Treatment Group, a CCOP Research Base, provides a framework for ongoing collaboration with my academic colleagues, an occasion to attend semiannual group meetings, and the opportunity to stay informed about new developments in oncology.

Why do I participate?

1. I want to help improve cancer care.
2. I want to be able to offer my patients the most up-to-date treatment possible.
3. I want to be part of a collaborative process with academic physicians to continue my professional development and learn about new developments in oncology.

Division of Cancer Prevention

Featured Clinical Trials

02.01.05 | Chemoprevention Trial for Head and Neck Cancer

Name of the Trial

Phase II Chemoprevention Study of Pioglitazone in Patients with Hyperplastic or Dysplastic Oral Cavity or Oropharyngeal Leukoplakia (UMN-0109M07254). See the protocol summary at http://cancer.gov/clinicaltrials/UMN-0109M07254.

Principal Investigator

Dr. Frank Ondrey, University of Minnesota Cancer Center

Why Is This Trial Important?

Head and neck cancer affects over 38,000 Americans each year, resulting in 11,000 deaths. Head and neck cancer sites are divided into the oral cavity, the oropharynx, and the larynx (voice box) and related structures. The oral cavity includes the lips and most of the soft tissue inside the mouth (for example, the gums and the main part of the tongue). The oropharynx includes the soft palate at the back of the mouth, the tonsils, and the base of the tongue. The larynx includes the voice box area and the entry tissues into the esophagus.

Leukoplakia, an abnormal patch of white tissue that forms on mucous membranes inside the mouth and elsewhere in the body, may be a precursor to head and neck cancer.

In this study, researchers are investigating the ability of pioglitazone, a drug used to treat type II diabetes, to reverse leukoplakia and prevent it from developing into head and neck cancer. Pioglitazone belongs to a new class of oral antidiabetic drugs called thiazolidinediones that have been shown to inhibit growth of some epithelial cancer cells.

"There is no current standard for screening or treatment of leukoplakia like there is for precancerous lesions of the colon, for example," said Dr. Ondrey. "We know that over the course of 5 years about 5 percent of patients with oral leukoplakia will develop invasive cancer, so it is important that we develop an effective means of treating the condition and preventing it from progressing to cancer."

Who Can Join This Trial?

Researchers seek to enroll up to 33 patients diagnosed with hyperplastic or dysplastic oral cavity or oropharyngeal leukoplakia. See the list of eligibility criteria at http://cancer.gov/clinicaltrials/UMN-0109M07254.

Where Is This Trial Taking Place?

This trial is being conducted at the University of Minnesota Cancer Center in Minneapolis.

Contact Information

For more information, call the University of Minnesota Cancer Center at 612-624-2620 or NCI's Cancer Information Service toll-free at 1-800-4-CANCER (1-800-422-6237). The call is completely confidential.

06.21.05 | Vaccine to Prevent Cervical Cancer

Name of the Trial

Phase II Randomized Study of SGN-00101 Vaccine in Human Papillomavirus-16-Positive Patients with Atypical Squamous Cells of Undetermined Significance or Low-Grade Squamous Intraepithelial Lesions of the Cervix (UCIRVINE-02-55). See the protocol summary at http://cancer.gov/clinicaltrials/UCIRVINE-02-55.

Principal Investigators

Dr. Bradley J. Monk, University of California, Irvine, and Dr. Dorothy J. Wiley, University of California, Los Angeles

fig. 7 | Dr. Bradley J. Monk, University of California, Irvine, and Dr. Dorothy J. Wiley, University of California, Los Angeles

Why Is This Trial Important?

Human papillomavirus (HPV) infection is common among women throughout the world. It is responsible for nearly all cervical cancers and most cell changes associated with low- and high-grade Pap test abnormalities.

Some types of HPV are associated with cervical cancer more often than others; for example, HPV-Type 16 (HPV-16) is found in half of cervical cancers worldwide. However, the vast majority of women infected with HPV-16 will never develop cervical cancer and will clear their infections spontaneously because of immune responses to the virus. Nonetheless, developing therapeutic interventions for viral infections associated with low-grade cellular changes may allow us to block the effects of HPV long before a precancerous change or a malignancy develops. In this study, researchers are testing a vaccine in women infected with HPV-16 who have LSIL or ASCUS Pap test results. The goal is to determine whether women who receive the study vaccine clear their infections and resolve their low-grade Pap testabnormalities more often than women who receive placebo (sterile water).

"Some women with HPV infections develop cancer because they don't seem to develop an appropriate immune response to the cancer-causing components of HPV," said Dr. Wiley. "We hope that this vaccine will help women develop that immune response."

Who Can Join This Trial?

Researchers seek to enroll approximately 140 patients aged 18 to 50 who have Pap tests showing ASCUS or LSIL. See the list of eligibility criteria at http://cancer.gov/clinicaltrials/UCIRVINE-02-55.

Where Is This Trial Taking Place?

The study is being conducted at the Chao Family Comprehensive Cancer Center at UC-Irvine and at UCLA's Jonsson Comprehensive Cancer Center.

Contact Information

See the list of study contacts at http://cancer.gov/UCIRVINE-02-55 or contact the NCI Cancer Information Service at 1-800-4-CANCER (1-800-422-6237). The toll-free call is confidential.

08.09.05 | Chemoprevention Study of Selenium for Non-Small-Cell Lung Cancer

Name of the Trial

Phase III Randomized Chemoprevention Study of Selenium in Participants with Previously Resected Stage I Non-Small-Cell Lung Cancer (ECOG-5597). See the protocol summary at http://cancer.gov/clinicaltrials/ECOG-5597.

Principal Investigators

Dr. Daniel David Karp, Eastern Cooperative Oncology Group; Dr. Omer Kucuk, Southwest Oncology Group; Dr. Randolph Marks, North Central Cancer Treatment Group; Dr. Michael R. Johnston, National Cancer Institute of Canada; Dr. Gerald H. Clamon, Cancer and Leukemia Group B; Dr. Steven Belinsky, Lovelace Respiratory Research Institute.

fig. 8 | Dr. Daniel David Karp, Eastern Cooperative Oncology Group

Why Is This Trial Important?

Lung cancer is responsible for more cancer deaths in America than breast cancer, colon cancer, and prostate cancer combined. In its earliest stages, non-small-cell lung cancer (NSCLC) may be removed surgically with potentially curative results. However, the incidence of a second tumor developing in patients who have been treated surgically for early-stage NSCLC is about 20 to 30 percent.

In this study, researchers are investigating the ability of selenium to prevent the development of secondary lung tumors in patients with surgically removed, early-stage NSCLC. Selenium is an essential dietary mineral that has been shown in animal studies to inhibit the growth of tumors. It is also associated with reduced cancer incidence in some animal populations.

"Selenium may help prevent cancer through a number of different mechanisms," said Dr. Karp. "It is an essential component of the antioxidant enzyme glutathione peroxidase, which protects tissue from oxidative damage and may help stimulate apoptosis (cell death). Selenium may also play an anti-inflammatory role by blocking the 5-lipoxygenase pathway."

Who Can Join This Trial?

Researchers seek to enroll 1,960 patients 18 years of age and older who have had stage I NSCLC completely removed by surgery. See the list of eligibility criteria at http://www.cancer.gov/clinicaltrials/ECOG-5597.

Where Is This Trial Taking Place?

Study sites in the United States and Canada are enrolling patients in this trial. See the list of study sites at http://www.cancer.gov/clinicaltrials/ECOG-5597.

Contact Information

See the list of study contacts at http://www.cancer.gov/clinicaltrials/ECOG-5597, or call the NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237). The call is toll free and completely confidential.

Division of Cancer Prevention

Cancer Research Highlights

1.4.05 | Lung Screening Study Shows What Happens after Positive CT Scan

Research has shown that low-dose spiral computed tomography (CT) is more sensitive than chest X-ray at detecting abnormal lung tissue. CT is so sensitive that it poses a risk for false positives in lung cancer screening. Furthermore, there are no standard recommendations for follow-up after positive CT. Researchers from NCI's Division of Cancer Prevention surveyed the outcomes after a group of 1,660 current or former heavy smokers who had quit within the last 10 years were randomized to receive the procedure and were referred to their personal health care providers for next steps. These individuals were participants in the Lung Screening Study, a pilot for the National Lung Screening Trial. The results of the follow-up of the positive results appear in the January 1 *Cancer*.

Of the 522 patients with a positive CT scan at baseline or 1 year after baseline, researchers found that the most common follow-up procedure was a second CT scan without biopsy (55 percent) followed by follow-up biopsy or comparison of current CT results with those from a prior X-ray or CT (12 percent). Four percent of patients underwent only a clinical examination and 3 percent received no follow-up. Of those who were not diagnosed with lung carcinoma, 45 percent were diagnosed with another condition as part of the follow-up. "These data may be useful in estimating the potential burden and cost of CT screening," the authors noted.

This story is available online at http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_010405/page6

1.25.05 | Cancer Biomarker Detection Method is Found Reliable

Investigators have created a reliable method to calibrate instruments across several different laboratories to detect potential cancer biomarker proteins with uniform accuracy, according to a study in the January 1 *Clinical Chemistry*. The method uses surface-enhanced laser desorption (SELDI) mass spectrometry (MS) to help clinicians detect protein biomarkers for prostate and other cancers.

The study was led by Dr. John Semmes of Eastern Virginia Medical School, and is part of a multi-institutional collaboration spearheaded by NCI's Early Detection Research Network (EDRN). Standard calibration algorithms for SELDI MS were established in six cancer research laboratories, including Dr. Semmes' lab at the Virginia Prostate Center, Fred Hutchinson Cancer Research Center, Johns Hopkins Medical Institutions, University of Alabama at Birmingham, University of Pittsburgh Cancer Institute, and University of Texas Health Science Center at San Antonio. Each lab then analyzed the same human serum samples—both cancerous and control—and obtained virtually identical protein expression profiles.

Dr. Sudhir Srivastava, NCI program officer and EDRN coordinator, noted that, "We established, for the first time, that mass spectrometry can yield reproducible output among different laboratories analyzing the same set of clinical samples." However, this is only the first phase of the study. In a follow-up study, NCI is testing the robustness of the developed algorithm in correctly classifying prostate cancers and controls obtained from multiple institutes in a blinded fashion.

If successful, the SELDI MS profiling of prostate cancer study may improve early detection of prostate cancer beyond the current utility of the widely used prostate-specific antigen test. However, Dr. Srivastava cautioned that any MS instrument must be carefully cross-validated for analytical sensitivity and precision before using it in the clinical setting.

This story is available online at http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_012505/page5

2.1.05 | Obesity Could Skew Test for Prostate Cancer

Obese and overweight men have lower levels of the blood protein prostate-specific antigen (PSA) that "could mask biologically consequential prostate carcinoma" when those men are given PSA tests for prostate cancer, according to a population study that published in the March issue of Cancer, and appearing in the journal's Web site (http://www3.interscience.wiley.com/cgi-bin/jissue/10992648l).

The study was conducted by Dr. Jacques Baillargeon and colleagues at the San Antonio Center of Biomarkers of Risk for Prostate Cancer, one of the NCI EDRN clinical and epidemiological centers.

Between 2001 and 2004, 2,779 men without prostate cancer were evaluated, comparing their blood serum PSA level with their body mass index (BMI), a standard measure for weight and obesity. PSA levels are already known to vary with an individual's race/ethnicity and age, but once these factors were controlled for, researchers also found a strict inverse relationship between weight and PSA levels. Thinner and fitter men had higher PSA levels than individuals with higher BMI scores.

According to the researchers, PSA levels appear to be suppressed by about one-third in men whose BMI scores are greater than 40. This tendency could lessen the value of the PSA screening test for overweight and obese men, producing false-negative results and delaying diagnosis of prostate cancer, the study concludes.

The PSA test is currently an FDA-approved, Medicare-reimbursed method of screening for prostate cancer among men over 50. Prostate cancer is the most common cancer in men, after skin cancer. Approximately 232,090 men in the United States will be diagnosed with the disease in 2005, and about 30,350 men will die from it.

This story is available online at http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_020105/page5

2.8.05 | False Positive Cause Some Men to Skip Subsequent Prostate Cancer Screening

Researchers have found that, among men undergoing a baseline round of prostate cancer screening, African Americans, men who have a high school education or less, and men with a false-positive baseline screen are less likely to return for subsequent screening. These findings are published in the January issue of *Cancer Epidemiology Biomarkers & Prevention*, and are based on 2,290 Caucasian and African American patients enrolled at the Detroit site of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

The researchers found that men who received false-positive test results at baseline were 1.9 times as likely not to return for subsequent screening appointments, compared with those who tested negative. African American men were 1.6 times as likely not to return for screening as Caucasians, and men with a high school education or less were 1.6 times as likely not to return as those with a post-high school education. A total of 184 patients did not return for their appointments, their reasons being refusal (61 percent), scheduling problems (29 percent), illness (4 percent), and travel out of the area (6 percent).

The authors concluded that when clinicians discuss prostate cancer screening with their patients, they should cover the likelihood of false-positives, the meaning of these results, the anxiety that may occur after receiving abnormal results, and the relationship between screening and mortality due to prostate cancer. “During the shared decision-making process, patients’ attitudes and perceptions should be ascertained,” they wrote. “This process could assist clinicians in ensuring that patients make informed choices about subsequent prostate cancer screening.”

This story is available online at http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_020805/page5#b

2.15.05 | APC Trial Safety Data Published: Increased Risk of Serious Cardiovascular Events Shown

Participants in a large colorectal cancer prevention study had an increased risk of serious cardiovascular events—cardiovascular death, heart attack, stroke, or heart failure—if they took the arthritis drug celecoxib (Celebrex) daily for an average of almost 3 years, according to an analysis released online by the *New England Journal of Medicine* on February 15. Celecoxib is one of several compounds that preferentially block one of two cycloxygenase (COX) enzymes that are produced in response to inflammation and by precancerous tissues. It was approved by the FDA for the treatment of osteoarthritis and adult rheumatoid arthritis in December 1998.

The participants in the Adenoma Prevention with Celecoxib (APC) Trial taking 200 mg of celecoxib twice a day had more than 2 times the risk of cardiovascular events, and those taking 400 mg of celecoxib twice a day had more than 3 times the risk of cardiovascular events compared with those taking a placebo twice daily. These results led to the December 2004 suspension of the drug within the trial, which was cosponsored by NCI and Pfizer, Inc., celecoxib's manufacturer. The APC Trial included more than 2,000 people with a history of precancerous colon polyps. It began in late 1999 and is scheduled to be completed this spring.

The effectiveness of celecoxib in preventing the recurrence of colon adenomas in APC participants is being analyzed. "The ability of celecoxib, or another agent that inhibits COX-2, to prevent colorectal cancer is an important question that remains to be answered," said Dr. Ernie Hawk, director of NCI's Office of Centers, Training, and Resources and project officer on the APC Trial. "The cardiovascular events seen in the trial were serious, but the total number of events was relatively small. The potential benefit of celecoxib to prevent cancer or to relieve pain must be weighed against this risk."

This story is available online at http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_021505/page5

3.1.05 | New Biomarkers May Improve Early Detection of Liver Cancer

Patients who have liver cirrhosis, an antecedent to liver cancer, can undergo frequent screening to catch cancer early, if it develops. But the current screening procedures for liver cancer, including ultrasound and blood tests (one of which detects alpha fetoprotein, or AFP), are not very reliable. However, researchers have identified a blood protein—des-gamma-carboxyprothrombin (DCP)—that may solve this problem, and NCI has launched a new clinical trial, led by Dr. Jorge Marerro of the University of Michigan and coordinated by Dr. Paul Wagner of NCI's Cancer Biomarkers Research Group, to determine whether an assay that detects DCP will improve the accuracy and sensitivity of liver cancer screening over the methods currently available.

DCP, a precursor to the protein prothrombin, is produced by the liver to help blood clot. DCP levels start to rise in patients with liver cancer, and this trend can be monitored through a blood test. The test kit, which was developed by Eisai Company and is being supplied to the study free of charge by this company, has shown 90 percent accuracy in detecting DCP.

Now the validity of that test will be measured through the EDRN-established phase II clinical validation trial conducted at six centers across the United States: University of Michigan; Mount Sinai Hospital in New York City; University of Pennsylvania; Mayo Clinic; St. Louis University; and Stanford University. Over the course of 2 years, researchers will monitor 450 patients who have liver cancer, 170 of whom are early stage, and a control group of 450 patients who have cirrhosis but not cancer. Data are expected in early 2007. "If DCP is proven as an early biomarker alone or as an adjunct to AFP," says Dr. Sudhir Srivastava, chief of NCI's Cancer Biomarkers Research Group, "it will trigger early intervention leading to a much needed effective clinical management of the disease."

This story is available online at http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_030105/page5#3

3.1.05 | Higher PSA Yields More Biopsies, Early PLCO Data Shows

Rates of biopsy among men with abnormal prostate-specific antigen (PSA) and digital rectal exam (DRE) tests show wide variance, according to some early data from the prostate cancer screening arm of the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial. Published in the March issue of the *Journal of Urology*, the study shows that at 3 years, of the 2,717 men who had a baseline positive PSA (greater than 4 nanograms per milliliter based on results from a central laboratory) at study entry, 41 percent had a biopsy within 1 year and 64 percent had a biopsy within 3 years. PSA scores of 7 ng/ml or higher were associated with significantly higher biopsy rates. Biopsy rates were lower among men who had positive DRE results but negative PSA results, with 27 percent of the 4,449 men in this category obtaining a biopsy within 3 years.

Diagnostic follow-up of PLCO participants was not included in the trial design, meaning that after screening, the decision for participants to undergo a biopsy or not was left to the discretion of treating physicians. Given the "large, geographically diverse sample of American men" participating in PLCO, said study lead author Dr. Paul F. Pinsky from NCI's Division of Cancer Prevention, "these results suggest that the experience of PLCO men in terms of follow-up biopsy is generally representative of current practice patterns in the United States."

A related commentary in the journal criticized the PLCO design for not requiring that participants undergo "effective therapy if cancer is found." In the study authors' published response, they explained that the design was necessary because "study investigators...work within a medical system of physician patient/autonomy, particularly those regarding the choice of diagnostic follow-up procedures or therapies." In addition, they argued, the study data "indicate that the medical community at large does not view immediate biopsy as the standard of care for all men with positive prostate cancer screens" and "clearly show that physicians are using clinical judgment in determining who should be biopsied."

This story is available online at http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_030105/page5#3

3.22.05 | PLCO Trial Publishes Baseline Findings

A multicenter randomized clinical trial to determine if screening for prostate cancer reduces mortality from the disease has published findings from the initial round of screening. The study is comparing men who receive annual prostate-specific antigen (PSA) testing and digital rectal exams (DREs) for 6 years with a control group that receives routine medical care.

"Everything about the study's findings should reassure people that the trial is on track and that if we are given enough time we will answer the question: Does prostate screening done in this way save lives?" says Dr. Gerald Andriole of Washington University School of Medicine. Because prostate cancer progresses slowly for many patients, he adds, it could take until the year 2019 to answer the question.

According to findings published in the March 16 *Journal of the National Cancer Institute*, of the 34,000 men in the screening group, about 7 percent had a positive DRE and about 8 percent had a positive PSA level. Of this group, 74 percent underwent additional diagnostic testing, and one-third had a prostatic biopsy within one year.

Overall, 1.4 percent of the men in the screening group were diagnosed with prostate cancer, most of which was clinically localized. A companion paper reporting on the first 3 years of this trial, which is part of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, appears in the March issue of the *Journal of Urology*.

This story is available online at http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_032205/page5

4.19.05 | Statin Use Linked to Lower Risk of Advanced Prostate, Colon Cancer

According to a large observational study presented this week at the AACR meeting, the use of cholesterol-lowering drugs, such as statins, may significantly reduce the risk of advanced prostate cancer.

Researchers at NCI, Johns Hopkins University, and Harvard University followed 34,428 U.S. men for more than 10 years. They found that men who used cholesterol-lowering medications had half the risk of advanced prostate cancer and a third of the risk of metastatic or fatal prostate cancer, compared with nonusers. The study did not reveal any effects of cholesterol-lowering drugs on localized prostate cancer.

"This is a promising lead on a class of drugs that may be offering unanticipated benefits, but we need further studies to confirm these findings as well as figure out the mechanisms at work," says Dr. Elizabeth Platz, the study's lead investigator at Johns Hopkins. More than 90 percent of the men who were using cholesterol-lowering drugs reported using statins in particular.

"The next steps will be to examine the relationship between statin use and prostate cancer recurrence, and to conduct studies involving prostate tissue to try to understand how statins might be preventing the progression of early prostate cancer," adds study co-author Dr. Michael Leitzmann of NCI's Division of Cancer Epidemiology and Genetics (DCEG).

Another study by researchers from Rutgers University, the University of Oklahoma, and NCI's Division of Cancer Prevention and CCR showed that a combination of atorvastatin (Lipitor) and celecoxib was more effective at limiting colon cancer development than higher dosages of either agent alone in a rat model. A dosage of 300 ppm of celecoxib and 100 ppm of atorvastatin inhibited 95 percent of the invasive and noninvasive tumors that developed in the untreated rats.

In contrast, twice the dosage of celecoxib given alone reduced tumor incidence and number by 80 percent; 150 ppm of atorvastatin alone reduced tumor incidence by 31 to 41 percent.

This story is available online at http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_041905/page5#e

5.17.05 | Low-Fat Diet may Lower Risk of Breast Cancer Recurrence

Significantly lowering dietary fat may lower the risk of recurrences of breast cancer in postmenopausal women treated for early-stage breast cancer, researchers reported at the ASCO annual meeting. The findings are from the NCI-sponsored Women's Intervention Nutrition Study, the first large-scale study to examine the influence of dietary fat on breast cancer outcomes in this population.

"This could be the first randomized controlled clinical trial of a lifestyle intervention that impacts breast cancer outcomes," said study lead author Dr. Rowan T. Chlebowski of the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center.

The 5-year study included 2,437 women, aged 48 to 79, drawn from 37 U.S. centers. The study group was placed on a low-fat diet, averaging about 33 grams of fat daily, while a control group consumed a standard diet that included approximately 52 grams of fat per day. Each group had previously received similar treatments for early-stage breast cancer, including mastectomy or lumpectomy with radiation, and postsurgical treatment protocols, depending on whether patients had estrogen-dependent cancers.

After 5 years, women on the low-fat diet showed a significant reduction in cancer recurrence compared with the control group: 9.8 percent vs. 12.4 percent. Women on the low-fat diet who had been previously treated for non-estrogen-dependent cancer—which is typically associated with a greater likelihood of recurrence—had a 42-percent reduced risk of recurrence compared with those on a standard diet.

"The effect on ER-negative disease is a surprising and potentially important observation regarding breast cancer," said Dr. Peter Greenwald, director of NCI's Division of Cancer Prevention. "These data demonstrate the possible importance of considering dietary factors in cancer therapy trials."

This story is available online at http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_051705/page5#c

7.5.05 | PLCO Publishes Sigmoidoscopy Results

Some 23 percent of the participants aged 55 to 74 in NCI's Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial have at least one polyp or mass in their lower colons, according to results from the largest study to date of flexible sigmoidoscopy. The study, published in the July 6 *Journal of the National Cancer Institute*, also found that 83 percent of participants who were offered sigmoidoscopy agreed to the procedure, which the authors characterize as a high rate of acceptance.

Starting in 1993, some 155,000 people enrolled in the PLCO Trial, which is being conducted at 10 centers nationwide. Half of the participants were offered screening sigmoidoscopy, and the other half maintained usual care with their own physicians. After the screening, patients with polyps or masses were referred to their primary physicians for follow-up. Twenty-eight percent of men were referred for follow-up visits, compared with 18 percent of women.

One year after the initial screening, 1.8 per 1,000 women and 2.9 per 1,000 men had been diagnosed with colorectal cancer, usually after colonoscopy and biopsy.

Women turned down sigmoidoscopy more often than men, with women older than 70 having the highest rejection rate.

Dr. Paul Pinsky, of NCI's Division of Cancer Prevention, said that the figures establish a benchmark for what could be expected if a large-scale flexible sigmoidoscopy screening program was undertaken in the United States. He said the study's large population and broad geographic catchment area, as well as the fact that diagnostic follow-up was carried out by independent health care providers not associated with the trial, make it more representative of actual practice than most other screening trials. However, he noted that the study population was somewhat less diverse and more educated than the U.S. population as a whole.

The PLCO Trial will eventually show whether screening reduces the death rate from the four cancers being studied.

This story is available online at http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_070505/page5

7.5.05 | Women's Health Study Finds No Anti-Cancer Benefit of Aspirin and Vitamin E

Taking low doses of aspirin every other day for 10 years did not protect women against cancer, the largest clinical trial of aspirin in cancer prevention has found. The dose was 100 mg every other day. Higher doses of aspirin may have protective effects, the researchers say, but increasing the dose could potentially lead to side effects in some individuals.

"The results at this time do not support the use of low-dose aspirin for cancer prevention," says Dr. Nancy Cook of the Brigham and Women's Hospital in Boston, lead author of the study published online in the July 6 *Journal of the American Medical Association (JAMA)*.

The findings are from the Women's Health Study, a randomized trial that evaluated the protective effects of aspirin and vitamin E on cancer and cardiovascular disease among 40,000 women aged 45 and over. Participants were free of cancer and cardiovascular disease at the start of the study.

No benefit was detected for the cancers examined, including breast and colon, but the researchers cannot rule out the possibility that aspirin may protect against lung cancer. Two studies in men have reported similar findings, but "the evidence for such an effect remains uncertain," the researchers write.

A companion report in *JAMA* from the Women's Health Study found no evidence that taking 600 IU of vitamin E every other day for 10 years protects women against cancer. "The best recommendation for the prevention of cancer and cardiovascular disease is to follow a healthy lifestyle," notes Dr. Cook.

This story is available online at http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_070505/page5#b

7.19.05 | Prostate Cancer PSA Testing Limitations Demonstrated

A large-scale study of prostate-specific antigen (PSA) screening for prostate cancer concluded that, contrary to current clinical practice, there is no definitive "cutpoint" PSA level to

determine the level of risk for the disease, according to an article in the July 6 *Journal of the American Medical Association*.

The study is based on an analysis of 8,575 healthy men who participated in the placebo arm of the Prostate Cancer Prevention trial; the men in the other study arm received finasteride. Researchers examined the receiver operating characteristic (ROC) curves of various PSA levels, which measures the relative sensitivity (percentage of true disease "positives" detected) and specificity (percentage of true disease "negatives" detected) of the screening method. They found that for detecting any prostate cancer, PSA cutoff values of 1.1, 2.1, 3.1, and 4.1 ng/mL yielded sensitivities of 83.4 percent, 52.6 percent, 32.2 percent, and 20.5 percent, and specificities of 38.9 percent, 72.5 percent, 86.7 percent, and 93.8 percent, respectively.

Study co-author Dr. Howard L. Parnes, chief of NCI's Prostate and Urologic Cancer Research Group, commented, "In the past, many clinicians felt that if the PSA value was below 4, men were essentially free of risk from prostate cancer. That is clearly not the case. Conversely, there was the belief if a man's PSA value was over 4, then a biopsy must be performed. That has also now come into question."

Dr. Parnes added, "It's good to remind people that at every level of PSA, the decision whether to have biopsy needs to be a thoughtful one that takes into account all of a man's risk factors."

This story is available online at http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_071905/page4

8.02.05 | NCI Analysis Reveals Critical Factors for Minority Trial Recruitment

An article in the August 1 *Journal of Clinical Oncology* by researchers in NCI's Division of Cancer Prevention shows how effective Minority-Based Community Clinical Oncology Programs (MBCCOPs) have been in boosting minority enrollment in cancer clinical trials, and outlines steps that could be taken to see higher enrollments in the future. NCI funds 13 MBCCOPs in 10 states, the District of Columbia, and Puerto Rico to increase the number of underrepresented groups in cancer clinical trials. Begun in 1990, these programs are part of the larger network of 63 NCI-funded CCOPs based in clinical research facilities.

Although MBCCOPs make up less than 20 percent of all CCOPs, they contribute 33 percent of the overall minority recruitment for all trials in the CCOP network, and 44 percent of minority recruitment to cancer prevention and control trials. In the early years of prevention and control trials (1995-1999), between 51 and 60 percent of the participants at MBCCOPs were minorities; by 2003, 80 percent of participants in these trials were minorities.

"The MBCCOP program has been successful in improving both the visibility of and accessibility to clinical trials in minority communities," said Dr. Worta McCaskill-Stevens, program director. "In addition to increasing minority participation in trials, the program holds great potential to contribute to minority-focused research in a number of ways."

Some of the most critical factors that influence recruitment of minorities to clinical trials within the MBCCOPs are the availability of protocols targeting the most common cancers seen in minority communities, the level of institutional support for minority recruitment, and issues endemic to the communities themselves, such as cultural barriers and access to transportation.

This story is available online at http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_080205/page5

9.20.05 | Anti-Seizure Drug Reduces Breast Cancer Hot Flashes

Hot flashes are one of the most common symptoms in women receiving treatment for breast cancer, especially hormone treatments such as tamoxifen. In a prospective, randomized, double-blind, placebo-controlled study of 420 breast cancer patients experiencing hot flashes, the anticonvulsant drug gabapentin reduced these symptoms by about half in some women. The multicenter study was based at the University of Rochester Medical Center in New York and published in the September 3 *Lancet*.

Nonhormonal treatments for hot flashes became a priority in 2002 when early results from the National Institutes of Health Women's Health Initiative showed adverse effects related to hormone replacement therapy, including increased breast cancer risk. Drugs such as the antidepressant venlafaxine and the antihypertensive clonidine are currently used to mitigate hot flashes. Lead author Dr. Kishan J. Pandya said in an interview that gabapentin now provides another good alternative, especially for patients already taking antihypertensives. Gabapentin is FDA-approved to treat epilepsy, and is also used for neuropathic pain.

The women in the study took a placebo, 300 mg of gabapentin, or 900 mg of gabapentin each day for 8 weeks and kept a diary to describe their hot flashes. The 900 mg dose produced significantly better results than the 300 mg dose after 8 weeks, reducing the frequency of hot flashes by 44 vs. 30 percent, and the severity by 46 vs. 31 percent. Other menopause symptoms among the three groups were not significantly changed, except for suppressed appetite and decreased pain in the 900 mg group of women.

This story is available online at http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_092005/page5#d

10.18.05 | Variation in *COX-2* Gene Assessed in Colorectal Adenoma Patients

The overall structure of the gene *cyclooxygenase 2*, or *COX-2*, may be an important determinant of the risk of colorectal cancer and may influence a patient's response to drugs that inhibit the COX-2 enzyme, according to researchers who conducted a pilot study of variations in the gene. Levels of the COX-2 enzyme often are elevated in colorectal and other cancers.

A large number of variants, or polymorphisms, in the *COX-2* gene have been reported. Using four polymorphisms in the *COX-2* gene, researchers in NCI's Division of Cancer Prevention (DCP) tested associations between the variants and the susceptibility to colorectal cancer and the responsiveness to aspirin and ibuprofen, two of the nonsteroidal anti-inflammatory (NSAIDs) drugs that nonselectively inhibit COX-2.

An interesting finding of the study is that some colorectal adenoma patients carrying certain *COX-2* polymorphisms benefited more from the use of COX-2 inhibitors than did other patients without the polymorphisms. The study, published in the October 17 *British Journal of Cancer*, included more than 700 patients with advanced colorectal adenoma and a matched group of controls. Future studies involving more patients and testing of additional polymorphisms are being planned.

"The results in this pilot study, especially the association with the widely used class of COX-2 inhibitors, are encouraging and if con-

firmed in future studies, would have significant implications in maximizing response and minimizing toxicity," says Dr. Iqbal Ali, the first author of the study.

This story is available online at http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_101805/page5#d

11.15.05 | Ovarian Cancer Screening With Ultrasound and CA-125 Finds Cancer, But Also Many False-Positives

A new NCI study shows that screening methods such as transvaginal ultrasound (TVU) and testing for the protein biomarker CA-125 can detect ovarian cancer, but can also produce many false-positive test results. The report on preliminary results from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial appears in the November 15 *American Journal of Obstetrics and Gynecology*.

These results, the first on ovarian cancer screening from the ongoing multicenter PLCO Trial, are based on analysis of the participants' initial screening tests. CA-125 and TVU have been considered potential screening techniques, but studies to date have not shown that they can be effective and thus they are not currently recommended. The long-term goal of the PLCO Trial is to determine whether screening with TVU and/or CA-125 decreases ovarian cancer mortality in women ages 55 to 74.

Of the 28,816 women who underwent baseline screening, 1,338 (4.7 percent) had an abnormal TVU and 402 (1.4 percent) had an abnormal CA-125 blood test. Thirty-four women (0.1 percent) had abnormal results in both screening tests. Among the women with abnormal test results, 29 tumors were detected, 20 of which were invasive cancers.

"Ovarian cancer is a disease that is often fatal, and both patients and physicians are anxious to find ways to detect it at an earlier, more curable stage," said lead author Dr. Saundra Buys of the University of Utah. "However, the results from the initial year of screening show that TVU and CA-125 cannot currently be recommended for widespread use in the general population."

This story is available online at http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_111505/page5

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