

## Advances in breast cancer research

RECENT studies on breast cancer have revealed a multitude of insights, developments, and advancements related to preventing and treating this disease. This overview focuses on selected studies that have been recently published or were presented at the American Association of Cancer Research (AACR) 2010 annual meeting.

### MANAGING TREATMENT-RESISTANT BREAST CANCER

New research takes multiple approaches to hard-to-treat breast cancers. In studies presented by teams of scientists from Georgetown Lombardi Comprehensive Cancer Center, researchers worked to formulate novel therapies based on a clearer understanding of treatment-resistant breast cancer cells.

“In our lab, we’re working on two approaches for overcoming breast cancers that are treatment resistant,” said Robert Clarke, PhD, DSc, one of the researchers and a professor of oncology and physiology and biophysics at Lombardi. “We’re after what works, even if [it] means taking the longer road. So, while it can be easier to find new combinations of existing drugs as a short-term approach, if we need to identify new targets and new drugs to get the best outcome for



A radiologist examines mammogram results.

patients in the long term, then that’s what we should be doing” (AACR 2010).

A second approach was explored by several researchers who presented the results of combination drug experiments designed to potentially serve as treatment for patients with resistant breast cancer.

In one study, researchers discovered that a combination therapy comprising trastuzumab and two investigational agents, pertuzumab and an antitubulin cytotoxic agent (DM1), was effective against breast tumors resistant to medical treatment (AACR 2010). In a second study, researchers reported that a taxane-bevacizumab combination appeared to be effective against hard-to-treat triple-negative breast cancer (AACR 2010). According to a third study,

presented by Neil O’Brien, PhD, a postdoctoral scholar in hematology/oncology at the University of California-Los Angeles, their findings suggests that treatment with lapatinib might be effective against breast cancer that has developed resistance to trastuzumab (AACR 2010).

### NEW FINDINGS IN CANCER GENOMICS

The identification of certain genes may help doctors offer patients tailored early recognition programs and individualized therapies; and in three recently presented papers, researchers investigated genes that confer high risks for breast cancer.

In one study, published in *Nature Genetics* (2010;42(5):368-369), researchers reported a 60% to 80% risk for breast cancer in women with mutations of the gene *RAD51C*. “These results reinforce our assumption that various rare gene mutations contribute to hereditary breast and ovarian cancer,” said lead investigator Alfons Meindl of the Technische Universitaet Muenchen.

In a second study, researchers at Fox Chase Cancer Center found that a protein called NEDD9 is critical in the formation of breast cancer tumors. In mice with aggressive breast cancer, researchers found that 89% of those with the *NEDD9* gene but only 29% of mice without the gene developed tumors over an 18-month period. “There is a lot of research describing contributors to cancer formation,

**The identification of certain genes may help doctors offer patients tailored early recognition programs and individualized breast cancer therapies.**

but it is always truly exciting when studies show that the loss or absence of something prevents cancer from occurring,” said Joy Little, PhD, a postdoctoral fellow who presented the findings at the AACR 2010 annual meeting.

A third study comparing genomic alterations in breast cancer cells found that the alterations affected genes that function as either oncogenes or tumor suppressors (AACR 2010). “If we find markers that can be significantly associated with patients [who] develop auxiliary metastasis, we can check for these markers at an early stage of the cancer management,” said Luciane Cavalli, PhD, an assistant professor of oncology at Georgetown Lombardi Comprehensive Center.

#### BIOMARKERS OF RISK

Although recent research has indicated that breast cancer risk factors differ among ethnic and racial populations (Hines LM et al. *Cancer*. Apr 26, 2010 [Epub ahead of print]), biomarkers are increasingly being used by researchers to help determine a women’s risk for breast cancer and develop strategies for prevention.

In several studies focusing on breast density change, teams of researchers found that increased breast density as seen on a mam-

**There may be detectable changes of proteins in blood within 2 years of making a clinical breast cancer diagnosis.**

mogram is linked to an increased risk of breast cancer. “These abstracts strengthen the observation that high breast density is associated with increased risk for breast cancer, and they strengthen the hypothesis that under some conditions, reducing breast density may be associated with reduced risk for breast cancer,” said Carol Fabian, MD, professor of medicine in the division of clinical oncology and director of the Breast Cancer Prevention Center at the University of Kansas Medical Center (AACR 2010).

When another group of researchers, led by Christopher Li, MD, PhD, from the Fred Hutchinson Cancer Research Center in Seattle, sought to discover and validate blood markers that could potentially be used for the early detection of breast cancer, they found that levels of epidermal growth factor receptor (EGFR) were significantly elevated in the blood of women within 17 months prior to their diagnosis (AACR 2010). “Our results suggest that there may indeed be detectable changes of proteins in blood within 2 years of making a clinical breast cancer diagnosis,” Dr. Li stated. “Identification of these proteins could have a major impact on our ability to detect breast cancer early, when it is most treatable.” ■

## FDA Update

The FDA approved the immunotherapeutic agent **sipuleucel-T (Provenge)** for the treatment of men with asymptomatic or minimally symptomatic metastatic, castrate-resistant (hormone-refractory) prostate cancer. The agent is designed to induce an immune response against prostatic acid phosphatase, an antigen expressed in most prostate cancers, and is the first in a new therapeutic class known as autologous cellular immunotherapies.

The FDA approved **erlotinib (Tarceva)** as a maintenance treatment for patients with locally advanced or metastatic non-small cell lung cancer whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.

The FDA approved a **reformulation of controlled-release OxyContin (oxycodone)** that has been designed to discourage misuse of the medication. The reformulation is intended to prevent the medication from being cut, broken, chewed, crushed, or dissolved to release more medication. It may reduce the risk of overdose caused by tampering and will likely reduce abuse by snorting or injection; but users can still ingest larger doses than are recommended.

## ESTIMATED NEW CANCER CASES, 2009

**219,440**

Lung & bronchus

**146,970**

Colon & rectum

**68,720**

Melanoma

Source: American Cancer Society. Cancer Facts & Figures 2009.

## Overdiagnosis in cancer needs to be addressed



© APHP-PSL/PHOTO RESEARCHERS, INC.

**SUBSTANTIAL** incidence of cancer overdiagnosis indicates a need for the development of clinical and research strategies to avoid unnecessary treatment and other harms, according to a review published in the *Journal of the National Cancer Institute* (2010;102(9):605-613). Using data obtained from large randomized screening

3-D CT shows a small colon polyp.

trials, researchers learned that about 25% of the breast cancers detected on mammograms and about 60% of the prostate cancers detected with prostate-specific antigen (PSA) testing could represent overdiagnosis. Further findings revealed that 50% of the cancers detected in a lung cancer screening trial utilizing chest radiographs and sputum testing may have represented overdiagnosis.

The authors explained that in addition to screening, other procedures, such as diagnostic imaging, may contribute to overdiagnosis. An example of such diagnostic imaging is virtual colonoscopy, which often detects extracolonic abnormalities that can lead to more tests and possibly overdiagnosis.

In response to their findings, the study's authors suggested strategies

to help quantify, recognize, and manage overdiagnosis in cancer. One strategy would involve educating patients on the risks and benefits involved with early detection. "Whereas early detection may well help some, it undoubtedly hurts others," the authors wrote. "Often the decision about whether or not to pursue early cancer detection involves a delicate balance between benefits and harms.... [D]ifferent individuals, even in the same situation, might reasonably make different choices."

Offered as another strategy to help reduce cancer overdiagnosis, researchers suggested conducting studies that could raise the threshold at which a screening test result is labeled *abnormal* or when further steps should be taken. ■

## Donated computer time can help conquer cancer

THE WORLD Community Grid (WCG) is currently using donated computer time to advance two cancer initiatives:

- **Help Conquer Cancer** Researchers involved with the Help Conquer Cancer project seek to a better understand and treat cancer through the use of protein X-ray crystallography. The WCG is aiding this initiative by processing the existing 86 million images of proteins that have gone through the X-ray crystallography screening pipeline at the Hauptman-Woodward Medical Research Institute (HW) in Buffalo, New York. Without the WCG, analyzing the existing pictures

would require almost 100,000 years. Improving the pipeline for protein crystallography will allow researchers to more quickly determine the structure of many cancer-related proteins. Researchers hope that this will lead to a better understanding of protein function and enable the development of potential pharmaceutical interventions to treat cancer.

- **Help Fight Childhood Cancer** This project is dedicated to finding novel drugs to treat childhood cancers, particularly neuroblastoma. Researchers at Chiba Cancer Center Research Institute and Chiba University are using the WCG to simulate



X-ray crystallography can be used to determine protein structure.

laboratory experiments to test 3 million compounds to determine which ones block three proteins expressed at high levels or abnormally mutated in aggressive neuroblastomas. In the absence of the WCG, researchers note that their investigation would take approximately 8,000 years to complete. Fortunately, the WCG will reduce the time required to conduct analysis to about 2 years.

For more information about these projects and other scientific research projects being aided by the WCG to benefit humanity, readers are invited to visit [www.worldcommunitygrid.org](http://www.worldcommunitygrid.org). ■

## Conflicting studies on statins and colon cancer

STATIN use may not protect high-risk persons against colon cancer and may even increase the risk of precancerous lesions, according to a subset analysis of a large prevention trial presented at the 2010 meeting of the American Association for Cancer Research (AACR).

According to the researchers, “preclinical studies had suggested that statins inhibit cancer development, but observational studies in humans and meta-analyses produced conflicting results that included a suggestion of increased cancer risk in statin users.” Results of the study reported at AACR revealed that not only did statin users have a nonsignificant 24% increased risk of adenomas during

5 years of follow-up but this also increased to 40% with long-term use (more than 3 years).

In commenting on the study, John Baron, MD, of Dartmouth University noted that although most studies to date have shown no evidence of a chemopreventive effect with statins, researchers at New York-Presbyterian Hospital/Weill Cornell Medical Center have discovered genetic variance in cancer protection from statin drugs. Their study, which was published in *Cancer Prevention Research* (2010;3(5):597-603), involved a genetic test used to help determine in which patients statin drugs might have the most benefit in reducing the risk of colorectal

**About 44% of whites taking statins were likely not protected against cancers because of an inherited variant.**

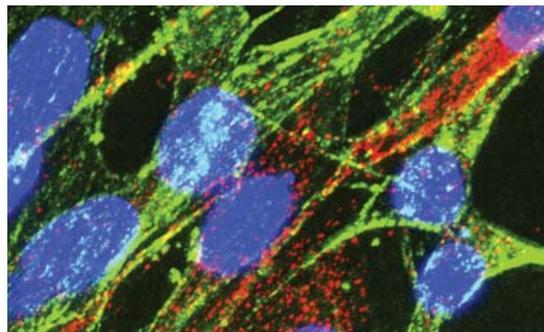
cancer. They found that genetic variation prevented the chemoprotective benefits of statin drugs; specifically, about 44% of whites taking statins were likely not protected against cancers because of an inherited gene variant.

“Carriers of the A allele express more of the full-length protein that binds statins, and are therefore more sensitive to statins and are more likely to experience the colorectal cancer risk reduction associated with long-term use,” said the study’s co-lead author, Steven Lipkin, MD. “We anticipate that genotyping for these alleles in patients may help identify those who are most likely to benefit from statins.” ■

## Toward targeted treatments for brain cancer

SEVERAL recently published studies have provided new findings on glioblastoma.

In one study, published in the *Annals of Neurology* (doi:10.1002/ana.22036), researchers at the University of Bonn examined residual glioblastoma tumor cells remaining after surgery and found that several fundamental properties of these cells were substantially different from those of cells from the midst of the tumor mass. “The cancer cells in the vicinity of the tumor have different properties compared to those from the center of the tumor,” explained Martin Glas, MD, from the Department of Neurology’s clinical neurooncology unit. “For instance, they are more mobile, they form other receptors, and they react differently to radiation therapy or chemotherapeutic substances.”



**Glioblastoma cells seen in a fluorescent light micrograph**

In a second study examining the biology of glioblastoma tumor cells, researchers focused their study on DNA methylation of a specific set of genes and discovered molecular factors that define subgroups of glioblastoma (*Cancer Cell*. 2010; doi:10.1016/j.ccr.2010.03.017). “Such findings are critical to the detection and treatment of brain cancer based on the genetic or epigenetic profile of

each patient’s disease,” said Francis Collins, MD, PhD, director of the National Institutes of Health. “The depth and breadth of expertise in The Cancer Genome Atlas research network, combined with ever-improving genomic technologies, is generating remarkably detailed insights into cancer.”

A third study, which focused on targeted treatments for recurrent or refractory anaplastic astrocytoma, found that patients treated with a targeted drug called trabectedin—an inhibitor of transforming growth factor-beta 2—had improved survival (39.1 months) compared with those treated with conventional chemotherapy (21.7 months) (AACR 2010; abstract 3716). Some patients had survived for as long as 8 years. ■