Symposium Proceedings

A Report on The California Breast Cancer Research Program's 6th Symposium

September 7–9, 2007

From Research to Action:
Breaking New Ground

CALIFORNIA
Breast Cancer
Research Program

Highlights of
From Research to Action: Breaking New Ground

A Report on the

California Breast Cancer Research Program's 6th Symposium

September 7–9, 2007 | Los Angeles, California

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A Message from the Director

We are pleased to provide this summary of the presentations made at the California Breast Cancer Research Program's sixth symposium, "From Research to Action: Breaking New Ground."

Held in Los Angeles, September 7–9, 2007, the symposium brought together nearly 600 scientists, health care and social service professionals, and women whose lives have been affected by the disease. Together, they heard and saw the progress that CBCRP-funded researchers are making against breast cancer and received an update on breast cancer research overall.

The CBCRP is truly a model nationwide. Over the past 13 years, we have provided over $180 million to scientists—and communities of women affected by the disease—to pursue innovative research.

This symposium provided an opportunity for all of us to pause and reflect. It was a time to acknowledge both the progress our researchers have made and the impact that breast cancer still has on our lives. We came together, with enthusiasm and intensity, to create new hope and optimism for a future without breast cancer.

Introduction

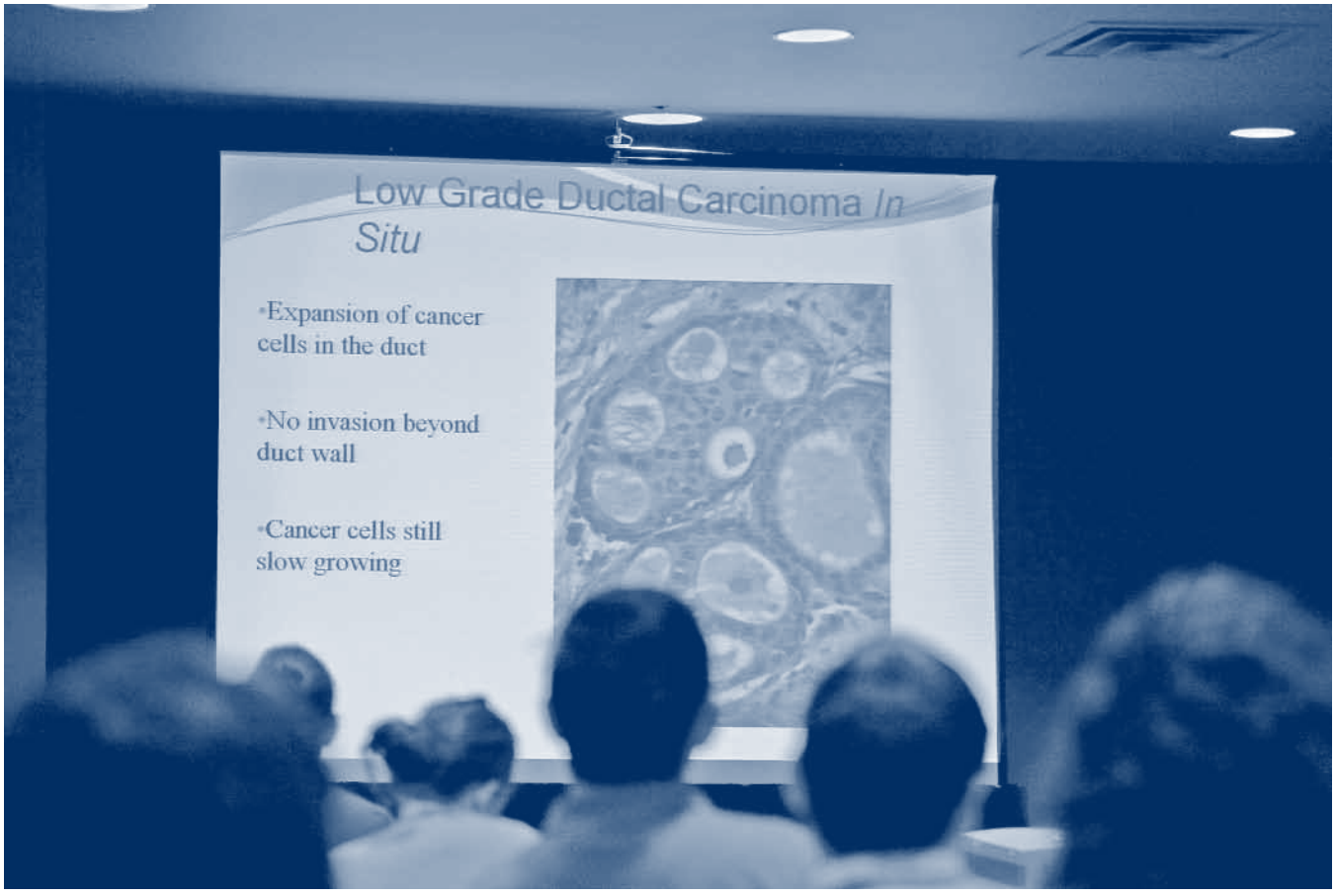
- A discovery that may spare the majority of women with breast cancer from one of the more toxic chemotherapies.
- The dawn of the age of individualized treatment based on the unique molecular and genetic characteristics of each woman's tumor.
- A call for action to get breast cancer-causing substances out of the environment.

These were some of the topics presented and discussed at our sixth symposium.

We are committed to getting the results of our funded research out to as many people as possible. In addition to making the results available on the Internet and through print publications, every two years we hold a statewide symposium, free to the public, where researchers present the results of their CBCRP-funded studies.

Roughly half of our attendees are researchers, and half are healthcare providers and members of the public. We make a special effort to bring women who have, had, or are at risk of breast cancer to the symposium. Eighty-two breast cancer survivors received scholarships that covered their travel and accommodations. The attendee diversity leads to spirited exchanges of ideas between researchers and the people most affected by breast cancer, as well as increased networking opportunities.

To continue these conversations about our research with a wider public, we are providing this report of summaries from presentations made at "From Research to Action: Breaking New Ground." It gives a capsule look at a conference that expressed our urgency to put research into practice—and our commitment to more effective diagnosis, treatment, and prevention to end the suffering caused by breast cancer.



Trends and Opportunities for Breast Cancer Research

Racial and Ethnic Disparities in Breast Cancer

For decades, researchers have known that some groups of women are at greater risk for getting breast cancer, and others are at higher risk of dying from it. Finding the reasons is one of the two main goals of the California Breast Cancer Research Program's Special Research Initiatives. This session featured two eminent experts who are providing leadership to the Special Research Initiatives.

Olufunmilayo (Funmi) Olopade, M.D., F.A.C.P., of the **University of Chicago Medical Center,** is internationally renowned for her expertise in cancer genetics and breast cancer predisposition. Genes, she said, provide the background for predisposition to breast cancer. But even more important roles may be played by personal health beliefs, health systems factors, and the environment. To untangle the causes, we need to understand the basic biology and genetics of the disease.

Breast cancer is not one disease. Researchers have identified a number of subtypes that have different patterns of genes. For example, Dr. Olopade treated one woman whose tumor doubled in size in two weeks. This woman had a "triple-negative" breast tumor, a type that does not have unusually high amounts of receptors for the hormones estrogen or progesterone, or unusually high amounts of another body protein, HER-2. Triple-negative breast tumors are difficult to treat and more likely to be deadly. Dr. Olopade's patient quit chemotherapy because she couldn't tolerate it, and died within six months. Another one of her patients has a tumor dependent on the hormone estrogen (ER+ tumor) that grows so slowly, it can be shrunk with a small pill. These extremely different tumors highlight how genetic profiles can be analyzed to predict prognosis. In the future, we may understand each case as an individual, the result of how a particular woman's genes interact with her environment to produce her breast cancer.

African American women in the U.S., particularly young African American women, are more likely to get "triple negative" breast cancer. Dr. Olopade conducted research in Nigeria and Senegal and found that in these nations, too, the majority of breast tumors were fast growing and triple negative. Her research centers on why breast cancer is aggressive in young women of African ancestry. Genes may play a role. African Americans have the highest rate of as-yet-unclassified variations in their genes. There may be genes that predispose some women to breast cancer that have not yet been discovered, and the unclassified variations could help explain African American women's different breast cancer patterns.

Dr. Olopade's research team is also investigating non-genetic factors. For example, research with rats shows that those kept in a group live longer than those kept in isolation. This raises the question of whether the social conditions of racism and isolation can make a genetic predisposition to breast cancer even worse.

Social conditions play a large role in differences in health among various U.S. ethnic groups, according to **David R. Williams, Ph.D.,** of **Harvard University.** He is a leading authority on socioeconomic and racial differences in health and the ways in which religious involvement can affect health. The higher breast cancer death rate for African American women needs to be understood in the context of other diseases, Dr. Williams said. In the U.S., African Americans have higher death rates than whites for 12 of the 15 leading causes of death, and lower rates for only three. There is a racial gap in health care from the cradle to the grave. African Americans and American Indians have elevated death rates in early, middle and late life. "As a society, we have failed to reduce health disparities," said Dr. Williams. "And this is not for lack of trying. What we have done in the past hasn't worked, and to reduce disparities in breast cancer, we will have to do something different."

There is a racial gap in health care from the cradle to the grave.

In 1950, African Americans had a lower death rate for all cancers than whites. The death rate for both groups increased over time, but for African Americans, the increase has been faster. African American women ages 35–44 have twice the breast cancer death rate as white women of that age group. This pattern is not unique to breast cancer. In general among Americans, the higher the mother's level of education, the lower the rate of infant mortality. But the most educated and advantaged African American women have a higher risk of infant mortality than the least educated and advantaged white women. This pervasive pattern of excess risk is not just genes, Dr.

Williams says, but it is due to the social environment. Racial residential segregation is a fundamental cause. Segregation affects health by:

- Determining the quality of education and job opportunities available in segregated neighborhoods;
- Creating pathogenic neighborhood and housing conditions;
- Constraining the practice of healthy behaviors and encouraging unhealthy behaviors, through, for example, the availability of fresh vegetables or exercise opportunities in the neighborhood.

Research also suggests that the quality of medical care is worse in segregated neighborhoods.

The level of segregation in U.S. cities today is only slightly lower than that in South Africa under apartheid. Of the 171 largest U.S. cities, there is not one where the conditions in which African Americans live are similar to those in which whites live.

Groups living under disadvantageous conditions make biological adaptations to these conditions. In this way, the environment shapes biology. Discrimination can affect physical health; a dramatic example came in the six months after September 11, 2001. There was an increase in low-birth-weight and pre-term births only among a group subject to much harassment during that time—Arab Americans.

Inequities in medical care also play a role. African American women get diagnosed for breast cancer later in the course of the disease, and they are treated less aggressively. This is true across most other diseases. But even if African Americans had equal access to medical care, Dr. Williams said, there would still be health disparities. “Medical care is about when you get sick. Social conditions affect whether you get sick.”

Dr. Williams suggested three ways to overcome health disparities resulting from discrimination. First, health practitioners can intervene to help their patients reduce stress and deal with the challenges of their socio-economic environment. This will help patients better manage their health conditions. Second, each of us needs to become active as an agent of change to deal with discrimination and racism in society. Third, regardless of socioeconomic status, each individual needs access to the highest quality medical care.

Trends and Opportunities for Breast Cancer Research

New Directions in Breast Cancer Treatment

Individualized breast cancer treatment holds the promise of being more effective. It could also free women from having to undergo treatments that they may not need or that may not work against their tumors. Researchers are making progress toward individualized treatment, according to **Joe W. Gray, Ph.D.,** of **Lawrence Berkeley National Laboratory.** Scientists now have a detailed understanding of how molecules interact within both normal cells and cancer cells. Some of these molecules transmit molecular signals from within and outside the cell. An example of these signaling molecules is HER-2. Some tumors have genes that cause the cells to make more HER-2 than normal cells, and medication to block HER-2 stops tumor growth. Many cancers have several abnormal signaling molecules. Scientists have developed methods to scan a cell for mutations and abnormal levels of signaling molecules. Within a few years, it will be possible to make millions of measurements on each tumor.

Will women actually be able to get the individualized treatments and better diagnostic tests that are just around the corner?

Tumors that look similar on a pathologist's slide look dramatically different in molecular composition. Molecular measurements can be used to determine which patients will respond to current therapies, and to develop therapies for those who won't respond. However, progress is slow, Dr. Gray said, because researchers are not linking the molecular analysis of tumors to testing of new medications in humans.

Dr. Gray is developing a tool that will allow researchers to test a new drug and predict the molecular structure of tumors that would respond to the drug. This tool could lead to more and cheaper clinical trials (tests of experimental treatments in humans), because the trials can be focused on patients where the chance that their tumor will respond is highest. Dr. Gray predicts that by linking treatments to the molecular analysis of each tumor, individualized breast cancer therapy will be available within a decade.

Thea D. Tlsty, Ph.D., of the **University of California, San Francisco,** described research aimed at overcoming a major inadequacy of current breast cancer diagnostic methods. Hundreds of thousands of women in the U.S. are diagnosed each year with one of two pre-cancerous conditions, ductal carcinoma in situ (DCIS) and benign breast disease. Each can be an early sign of invasive breast cancer, but only for a minority of women who have it. For example, half of women with DCIS will have no future disease if they get no treatment. Moreover, in some women, DCIS will progress to invasive breast cancer despite the current standard treatment. Some women are being over-treated, and others under-treated, and there's no method to identify who needs treatment and who does not.

Scientists have searched without success for a molecule that might be present at higher—or lower—levels in DCIS cells that progress to invasive breast cancer than in those that do not. Dr. Tlsty's lab has made progress toward a test for a "molecular signature," a combination of abnormal levels of several molecules that, when they are all present together in a cell, can predict whether it will later form a tumor. So far, they have found one molecular signature that predicts with 98 percent accuracy whether cells will progress to cancer, and another that predicts with 93 percent accuracy whether cells won't.

But will women actually be able to get the individualized treatments and better diagnostic tests that are just around the corner? That's the question raised by **Musa Mayer,** an 18-year breast cancer survivor, advocate, and author of three books on the disease. Financial interest has a distorting influence on research, she said, and that creates an ever-enlarging disconnect between what science is making possible and the current reality.

Progress toward individualized treatments may be slower than predicted. To see if an AIDS drug is working, researchers can measure a patient's viral load. With breast cancer, researchers have to wait and see if disease recurs and if patients who receive treatment live longer. "A marker for survival would revolutionize breast cancer research," said Ms. Mayer.

Most medications only work on ten percent of breast cancer patients. One reason for the lack of tests to see who will respond, Ms. Mayer said, is that drug companies have no incentive to shrink the pool of people treated. With the drug Herceptin, researchers co-developed a test that predicted which tumors the drug would treat, resulting in a therapy targeted

only to tumors that test positive for abnormally high levels of the HER-2 protein.

"We are perhaps witnessing the dawn of an era of medicine that spares patients treatments they don't need," said Ms. Mayer, "but people are afraid that if better treatments come, they won't be able to afford them. Do we, as a society, have the will to enact what every other developed country offers its citizens: universal health care?" She quoted former U.S. Surgeon General David Satcher, who said that equalizing the death rates of whites and minorities during the 1990s would have saved more lives than all the technological breakthroughs of those years. At the threshold of the molecular age, Mayer said, anything seems possible. But how many breast cancer patients might benefit from full access to the tools we already have?

Marisa Weiss, M.D., oncologist and founder of **breastcancer.org,** began her talk dressed in a white lab coat. Saying she wanted to approach the question of a doctor visit from the patient's viewpoint, she quickly disrobed to bare feet and a hospital gown. "Now when," she asked, "would you choose to wear something like this to an important meeting about your future?" A person with a serious illness is entrusting her or his life to an M.D. during a medical appointment. But the way each party is dressed, and the meeting being held on the doctor's turf, both lead to a power imbalance. Dr. Weiss provided some tips for changing these dynamics during the seven minutes of face-to-face time available during the average doctor visit for a serious illness. Her tips included:

- If your doctor doesn't begin by washing her or his hands, it can be effective to say, "I love it that you, unlike some other doctors, always wash your hands." The doctor will usually head right for the sink.
- Since it is hard to remember life-and-death information your doctor may provide, and since taking notes cuts down on communication, you can bring a supportive friend or relative to take notes. Make clear to your doctor what information you want revealed to this person.
- Have your support person leave the room during the physical examination, and ask your most personal questions at that time.

Trends and Opportunities for Breast Cancer Research

Keynote Address: "And From Action to Research"

"The serial killer known as breast cancer may be claiming fewer victims this year than last year," and it may be because women have less exposure to estrogen from outside their bodies, said **Sandra Steingraber, Ph.D.** An ecologist, author and cancer survivor, Dr. Steingraber is an internationally-recognized expert on environmental links to cancer and reproductive health. She said that American women's use of estrogen-containing hormone replacement therapy has dropped by 75 percent, and that evidence links this drop to a slight decrease in the number of breast cancer cases being diagnosed in the U.S. each year.

However, women in this country are still being exposed to estrogen-like chemicals found in cosmetics, pesticides, plastics, and many other products. Two widely-used chemicals that show evidence of causing changes in breast tissue that can lead to breast cancer are the pesticide atrazine and the plastic ingredient bisphenol A. It is impossible for women to stop their exposures to substances like these, because they are so pervasive in the environment, "so we can't conduct the experiment on what would happen to breast cancer rates if we cut atrazine and bisphenol A by 75 percent." said Dr. Steingraber. Only activists can make this research possible, she said, just as activists have made possible a long line of scientific discoveries about the environment and human health. These discoveries go back to activism that spurred the scientific work behind Rachel Carson's pioneering book exposing the dangers of pesticides five decades ago, *Silent Spring*.

Some research about the environment and breast cancer can only be conducted if activists make it happen.

"We need to keep up our activism until scientists can do the experiment, 'The Impact of Atrazine and Bisphenol A Abolition on Breast Cancer'." she said. The environmental struggle has become a human rights problem, and the biggest obstacle to progress is that people think the fight is too big. But she compared the fight for an environment that doesn't cause breast cancer to the fight for women's suffrage. A sustainable future is not inevitable, she said, but it can be won.

Trends and Opportunities for Breast Cancer Research

Workshops

The California Breast Cancer Research Program gathered experts from across the country and around the state to discuss the current status and possible new research directions of critical areas in breast cancer.

Breast Cancer Prevention Strategies

What can public health educators, policy makers, and women themselves do to prevent breast cancer? **Marilee Gammon, Ph.D.,** of the **University of North Carolina,** outlined modifiable risk factors for breast cancer, including:

- Surprisingly, age. Over age 50, in the U.S., a woman's risk for breast cancer goes up six-fold, but not in Japan or China. This means that whatever raises a woman's risk after age 50 in this country can be changed.
- Starting menstruation earlier than age 12.
- Late menopause.
- Giving birth at a late age.
- Never giving birth.
- Never lactating.
- Being overweight. Weight gain after age 50 especially increases a woman's breast cancer risk.
- Alcohol consumption, which can as much as double a woman's breast cancer risk. Alcohol use is going up among young women who are establishing lifelong habits, which could mean more breast cancer in the future.
- Use of oral contraceptives, which raises breast cancer risk slightly.
- Using hormone replacement therapy for ten or more years after menopause.
- Being physically inactive. It takes more activity after menopause than before to lower breast cancer risk.

Dr. Gammon suggested these breast cancer prevention guidelines for individuals, the healthcare system, and public health agencies:

- Reduce radiation exposures.
- Promote breast-feeding.
- Avoid hormone use.
- Reduce alcohol intake.
- Avoid weight gain.
- Increase physical activity levels.

One possible risk factor for breast cancer is smoking, or exposure to second hand smoke. **Peggy Reynolds, Ph.D.,** of the **Northern California Cancer Center,** described the biological evidence on smoke and breast cancer as mixed. Smoke contains cancer-causing chemicals that can move in the body into the breast. But smoking also inhibits some cancer-causing substances.

Surprisingly, age is a modifiable risk factor for breast cancer.

Dr. Reynolds is the investigator in the largest prospective study designed to investigate breast cancer, a research project among 133,479 retired California teachers she has conducted since 1995. In this study, women who had breast cancer were more likely to be current or former smokers than those who didn't have the disease. The women's risk for breast cancer increased with more smoke. The risk was also higher among women who started smoking before age 20 or who smoked four or more years before their first full-term pregnancy. Other research on smoke and breast cancer has produced mixed results. However, Dr. Reynolds said, "Since we know smoke is a risk factor for lung cancer and heart disease, it would be prudent to avoid it."

It might also be prudent to consume soy foods and green tea, based on research by **Anna H. Wu, Ph.D.,** of the **University of Southern California.** In a study Dr. Wu conducted among Chinese American, Filipino American, and Japanese American women in Los Angeles, after adjusting for other known breast cancer risk factors, a high intake of soy during the teen years reduced breast cancer risk, and a high intake during both the teen years and adulthood lowered the risk further. Studies by other researchers confirm these findings. Soy has substances called isoflavones that are similar to the breast

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cancer prevention drug tamoxifen. Dr. Wu cautioned that the soy foods Asian populations eat often have much higher levels of isoflavones than the more processed products available to Western populations.

Dr. Wu also found that drinking green tea reduces breast cancer risk, but drinking black tea does not. Green tea protects against breast cancer both before and after menopause, both for tumors that depend on hormones (ER+ PR+) and those that don't (ER- PR-). Green tea's protective effect comes from high levels of substances called catechins.

Less benign substances may be involved in the falling age of puberty among U.S. girls, which raises their future breast cancer risk. **Lawrence H. Kushi, Sc.D.,** of **Kaiser Permanente,** described ongoing research at four locations across the U.S., including his in the San Francisco Bay Area, into the possible role of exposures to chemicals from the environment in the falling age of puberty. Dr. Kushi's team has enrolled over 1,000 healthy girls ages 6–8. They are investigating the girls' exposures, through products such as shampoos and household practices such as pesticide use, to a variety of chemicals implicated in disruption of hormones or in causing cancer. Among the chemicals are PAHs (polycyclic aromatic hydrocarbons), which are found in cigarette smoke, grilled and smoked foods, and air pollution; polychlorinated biphenyls (PCBs), which were formerly widely used; PBDEs (polybrominated diphenyl ethers), which are found in flame retardants, clothing, and cars; and phenolics, which are found in many products. The researchers are also analyzing the girls' urine—and, when the girls agree, blood—for markers of environmental exposures, and using saliva or blood to assess the girls' genotypes.

So far, by year two of the study, 26 percent of seven- and eight-year-old girls show signs of puberty, with those at higher weight being twice as likely to do so. A pilot study has detected many of the chemicals listed above in the girls' bodies, with patterns of exposure varying among the four study groups of girls across the country.

Special Topics Involving Young Women with Breast Cancer

Three physicians with extensive experience treating and conducting research with young women who have breast cancer and a woman diagnosed with the disease at 32 addressed ways that breast cancer cause and treatment for women under 40 may differ from those for older women. **John S. Link, M.D.,** of **Breastlink Medical Group, Inc.,** provided some background. Although the number of women in the U.S. diagnosed with breast cancer has gone up over the last two decades, the percentage of younger women has remained fairly constant. Approximately five percent of U.S. women diagnosed with breast cancer (12,000 per year) are under 40, and half of those are under 30. Younger women get all the same types of breast cancer as older women, but younger women are more likely to have difficult-to-treat "triple negative" tumors. These tumors don't produce excess amounts of any of three cell proteins, estrogen receptors or progesterone receptors (which allow cells to take up each of those two hormones), or HER-2. Younger women diagnosed with breast cancer are also more likely to have mutations on their BRCA genes than their older counterparts. A breast cancer diagnosis for a woman under 40 typically begins with her finding a lump or nipple discharge herself; women over 40 typically have their breast cancer detected by a mammogram. However, the vast majority of breast lumps young women find are not cancerous.

Approximately five percent of U.S. women diagnosed with breast cancer (12,000 per year) are under 40, and half of those are under 30.

A hereditary risk for breast cancer makes it more likely that a woman will get the disease at a younger age, said **Carey A. Cullinane, M.D., M.P.H.,** of the **Long Beach Memorial Medical Center.** She explained that the normal versions of the BRCA1 and BRCA2 genes prevent tumors from developing. Five to ten percent of U.S. women have inherited a mutation that disables the gene's protective effect. By the time they reach age 50, 33–55 percent will have breast cancer, compared to two percent of women from the general population. Women with a hereditary predisposition also have a higher risk of recurrence after having the disease, 60 percent, compared to 20 percent for the general population. Dr. Cullinane recommends that women who have these mutations be

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screened yearly with an MRI (magnetic resonance imaging), starting at age 25. The MRI detects small tumors earlier than a mammogram among high-risk women, although the test's rate of false positives makes it less useful for the general population. Prevention options are few. One is breast removal, which reduces breast cancer risk substantially, but not completely. Second, the medications tamoxifen or raloxifene reduce risk by 50 percent, but raise the future risk of osteoporosis by causing loss of bone mass.

Genetic counseling can help women decide whether to have genetic testing, decide which tests to take, and understand test results. Women who should consider genetic counseling include those who have:

- Early-onset breast cancer;
- Cancer in both breasts;
- Ovarian cancer or a family history of ovarian cancer;
- A family history of male breast cancer, breast cancer before age 40, or ovarian cancer;
- Ashkenazi Jewish heritage, which carries a higher risk of BRCA mutations.

Men with breast cancer should also consider genetic counseling. Since each woman inherits one copy of the BRCA1 and BRCA2 genes from each parent, a woman's father's family history is as relevant as her mother's.

Younger women diagnosed with breast cancer often face the question of what chemotherapy will do to their future ability to have children. **James R. Waisman, M.D.,** of the **Breastline Medical Group, Inc.,** said two commonly-prescribed types of chemotherapy agents produce a high risk of infertility, especially with a long course of treatment. These are cytoxin and agents similar to it, and taxanes. When a young woman learns she has breast cancer, she's thrown into a crisis and faces many decisions. Adding a visit to a fertility specialist piles on more complications, but can lead to timely efforts to preserve her ability to bear children. The method with the highest success rate is harvesting the woman's eggs, fertilizing them in a laboratory, and preserving them for future implantation. The future pregnancy does not appear to increase a woman's risk for breast cancer recurrence. However, this expensive series of procedures is not covered by medical insurance. A method under investigation to preserve fertility is preserving a woman's eggs to be fertilized and implanted at a later date. This has been less successful than preserving embryos, because eggs are more fragile. Other methods under investigation include preserving the woman's ovarian tissue for transplant after cancer treatment is completed, and using medication to "put the ovaries to sleep" during chemotherapy. The latter method works by keeping the ovaries from going through development, so they dodge chemotherapy's effect on fast-growing cells.

Using medication to suppress the ovaries worked for one of the workshop's presenters, **Heather Himelwright,** who gave birth to a healthy baby four years after completing chemotherapy for breast cancer. Diagnosed at 32, Ms. Himelwright had been an insurance broker for ten years. She'd turned down customers because of their medical histories, "and I thought, I'll never get life insurance or health insurance again." She decided to use her insurance expertise to benefit people with cancer, and started a company, **Cancer Patient Insurance Advocates,** to help patients with insurance issues. She helps people who have cancer find insurance, maximize their current insurance benefits, and handle disputes with insurers. Many people with cancer fear that to keep medical insurance, they will need to stay with their current employer for the rest of their lives. Ms. Himelwright helps people steer through federal and California state programs that guarantee continued coverage, but only if they are accessed in a timely fashion.

Estrogen, Progesterone, and Breast Cancer

In 2001, the Women's Health Initiative Study, a large nationwide study following tens of thousands of women, reported that the therapy most widely used to relieve symptoms of menopause raised women's risk for breast cancer. Use of that hormone replacement therapy, a combination of the hormones estrogen and progesterone, plummeted. In 2003, the breast cancer diagnosis rate in the U.S. declined steeply, with 10,000 fewer cases. The rate stayed at that lower level during 2004. **Adrian Lee, Ph.D.,** of **Baylor College of Medicine,** said evidence has accumulated that the drop in use of hormone replacement therapy caused the drop in breast cancer incidence. First, the decline was for tumors that produce excess estrogen receptor proteins and depend on estrogen to grow. The incidence of diagnoses of estrogen-receptor-negative (ER-) tu-

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mors did not change in 2003–2004. When the 2003 decline was first reported, some critics said it was the result of fewer women having screening mammograms. But a subsequent study found that even among women who were screened, there were fewer cases of breast cancer diagnosed.

Dr. Lee pointed out that many factors that raise or lower breast cancer risk are related to hormones. Some of these are having the ovaries removed or a pregnancy at a young age, which lower risk, and having dense breasts or gaining weight after menopause, which raise risk. Therefore, modifying a woman's hormone levels can impact her risk for breast cancer.

Earlier versions of hormone replacement therapy used estrogen alone. However, this led to cells in the lining of the uterus growing and dividing in ways that could develop into cancer (hyperplasia). Adding progesterone cancelled the effect of estrogen on the uterus and blocked abnormal cell growth. But the hormones affect the breast and uterus in different ways. In the breast, progesterone combined with estrogen causes cells that line the ducts to grow and divide abnormally.

Exposure to higher-than-normal levels of estrogen during fetal development raises a woman's future risk of breast cancer, but during childhood, it lowers her future breast cancer risk.

A key to how estrogen is involved in breast cancer may be the chemical structure of the estrogen receptor, the protein that combines with estrogen and allows cells to take estrogen in. The estrogen receptor also interacts chemically with a variety of other proteins produced by the body. These interactions lead to changes in the cell. When the estrogen receptor combines with estrogen, the two proteins can enter the cell nucleus and affect the cell's DNA. The estrogen receptor's ability to interact with so many proteins and ability to enter the cell nucleus may make it interact chemically with environmental toxins, and serve as a conduit to bring those toxins into contact with cellular DNA.

Women who need hormone replacement therapy may still be able to take estrogen alone, according to **M. Ellen Mahoney, M.D., F.A.C.S.,** of the **Community Breast Health Project.** "According to the media, estrogen is bad, period, but the reality in the clinic is more complex," she said. A woman can take estrogen therapy, and her physician can monitor her uterus for abnormal cell growth (hyperplasia). Many women do not form hyperplasia, and they can continue estrogen therapy safely.

Leena Hilakivi-Clarke, Ph.D., of **Georgetown University,** described how timing of exposure to estrogen affects a woman's risk for breast cancer. Lifetime exposures to high levels of estrogen increase a woman's breast cancer risk, but the picture is more complicated for estrogen exposures at critical stages of breast development. Several markers indicate that a woman was exposed to high hormone levels as a fetus, when the breast goes through its first critical stage of development. One of these markers is high birth weight, which is linked to an increased risk for breast cancer. On the other hand, a marker for high exposure to estrogen during childhood is having been plump and short, which reduces a woman's risk for breast cancer. These different effects of high estrogen exposures at different times raise the question of whether exposure to estrogenic compounds from the environment might raise or lower a woman's breast cancer risk, depending on when the exposure occurred. Animal studies provide some clues as to why excess estrogen exposure during fetal development raises breast cancer risk. Exposing rat fetuses to excess estrogen leads to the adult rat having increases in the activity of genes that make cells survive, and a reduction in the activity of genes that suppress tumors. These changes are epigenetic, meaning that the genes are not mutated but are instead turned on or off by chemical changes in nearby DNA.

During another critical period of breast development—pregnancy—exposure to normally-occurring high levels of estrogen carries a dual risk. If the exposure occurs in a first full-term pregnancy before the woman is 20, she has a 50 percent reduction in risk. For a first child over age 30, her lifetime risk increases. In animals, estrogen provides the protective effect conferred by pregnancy. But in humans, women who had markers for higher-than-normal exposure to estrogen during pregnancy—severe nausea, infants born weighing more than nine pounds, excessive weight gain—later have a higher risk of breast cancer. Women with elevated levels of progesterone during pregnancy have the lowest subsequent breast cancer risk.

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Eva Lee, Ph.D., of the **University of California, Irvine,** presented research pointing to anti-progesterone medications as possible breast cancer preventives. The normal version of BRCA1 is involved in suppressing tumors; in the mutated version, this function of the gene is turned off. Women with BRCA1 mutations have a high breast cancer risk, but men with the same mutation do not. However, both men and women with BRCA2 mutations have a high breast cancer risk. This means that female hormones are likely involved in increasing the risk of a mutated BRCA1 gene. Research with mice showed that when BRCA1 is mutated, cells do not have their normal ability to destroy progesterone after using it. The resulting increase in the amount of progesterone in the cell appears to be important for tumors to form. Giving mice with mutated BRCA1 genes low doses of the anti-progesterone medication mifepristone (the same medication used in higher doses in medical abortions) blocked the formation of mammary tumors, the mouse equivalent of breast tumors. In the future, low-dose anti-progesterone medications may be used to lower breast cancer risk without the side effects of currently-used anti-estrogens (aromatase inhibitors and tamoxifen). Possibly, anti-progesterone therapy could even prevent tumors in women with BRCA1 mutations.

Complementary and Alternative Medicine

Women with breast cancer have put alternative medicine on the map, according to **Beverly Burns, M.S., L.Ac.,** of the **Charlotte Maxwell Complementary Clinic** and **Osher Center for Integrative Medicine.** Breast cancer patients used alternative healing, leading scientists to study these healing methods. Now, university-based treatment centers include such formerly alternative treatments as acupuncture and yoga. The National Institutes of Health's terminology is changing from "alternative," meaning "instead of," to "complementary," meaning, "along with."

Complementary medicine spans a wide variety of practices, including:

- Mind/body medicine.
- Herbs.
- Manual therapy, such as massage, acupuncture, and chiropractic.
- Energy therapies, such as Reiki, Qi Gong, and therapeutic touch.
- Bio-electromagnetics, such as light therapy, magnetic therapy, TENS units.
- Diet approaches, such as supplements and vitamins, the elimination diet, and the macrobiotic diet.
- Therapeutic exercise, such as yoga.
- Traditional medical systems, such as traditional Chinese medicine, Ayurvedic medicine, and homeopathy.

Most women with breast cancer combine conventional medicine with complementary therapies. Their reasons include believing that complementary treatments are safer and more natural; feeling treated as a whole person by alternative practitioners; and wanting the emphasis on well-being and prevention of found in complementary medicine.

Some types of complementary medicine are easier to research than others. Mind/body approaches get the most research funding, and the most-studied modality is prayer. Diets are difficult to study, because they involve complex variables. Herbs need to be evaluated for efficacy, to standardize doses, and to find out if they interfere with other treatments. Worldwide, 80 percent of the medicines people take are plant-based. There are over 20,000 herb-based medicines in use, but only 30 have been scientifically evaluated. New research methods are needed, and evaluating herbs can be complicated. For example, in Chinese herbal treatment, a prescription may include four to 24 herbs that work synergistically. Finding and isolating compounds in those herbs won't answer questions about the effectiveness of the combination. Moreover, diagnoses from traditional Chinese medicine don't match conventional diagnoses. A woman with breast cancer can have ten different diagnoses in Chinese medicine. An ideal clinical trial (research testing treatments on humans) would consider the diagnosis of the alternative system, and match treatments individualized to that diagnosis.

Two aspects of complementary medicine are difficult to research. The first is evaluating combinations of treatments as they are actually delivered in the community. The second is interactions, both among complementary treatments and with conventional treatments. Another complication is that relationships with providers are often an important part of com-

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plementary medicine, leading to different providers possibly getting different results because of different relationship effects.

Complementary medicine is a powerful tool for relieving symptoms of both cancer and cancer therapies. However, it is difficult to evaluate whether complementary treatments improve long-term outcomes. Some modalities have proven applications. For acupuncture, research data are as strong as for accepted Western therapies. Acupuncture relieves symptoms of cancer and cancer treatment, including nausea, pain, anxiety, depression, breathlessness, dry mouth after radiation, hot flashes from hormone-blocking therapy, post-chemotherapy fatigue, and constipation. Exercise during treatment decreases fatigue, decreases weight gain, and reduces the risk of post-surgical swelling of the arm. Exercise and diet can enhance quality of life post-treatment. Massage and therapeutic imagery can help with nausea associated with chemotherapy, with fatigue caused by cancer or chemotherapy, and with cancer pain.

Complementary medicine is a powerful tool for relieving symptoms of cancer and cancer therapies. However, it is difficult to evaluate whether complementary treatments improve long-term outcomes.

A number of supplements and herbs are good alternatives to hormone replacement therapy for hot flashes, including indole 3 carbinole, curcumin, green tea, conjugated linoleic acid, CoQ10, omega-3 fatty acids, vitamin D3, vitamin E, melatonin, and calcium. On the other hand, some herbs and supplements should not be used at the same time as some conventional breast cancer treatments. A number of herbs increase the risk of bleeding, so a wise precaution is to stop herbal treatments seven days before surgical procedures. Essiac should never be used during chemotherapy, because it might counteract the chemotherapy's effects. Anti-oxidants—such as vitamins A, C, and E, selenium, and melatonin—should not be used during chemotherapy and radiation, which work through oxidative mechanisms. A major problem with herbal treatments is that they are not standardized or regulated. Some have been found to be contaminated with toxic substances or adulterated with conventional over-the-counter medicines.

Ms. Burns provided guidelines for choosing and using complementary treatments:

- In California, where complementary practitioners are licensed, ask where the practitioner you plan to consult was educated and if she or he has a license.
- Find a complementary practitioner with extensive experience with cancer.
- Avoid anything that claims to affect a wide variety of diseases, or that makes a great claim, such as, "cures cancer."
- Avoid anything that is significantly less expensive than comparable treatments or items.
- Avoid anything promoted with pseudo-medical jargon, such as, "detoxify."
- Communicate with your M.D. about complementary therapies you use.

Advances from CBCRP-funded Research

Breakout Sessions

The CBCRP has invested over $180 million dollars in breast cancer research, resulting in advances on several fronts of the breast cancer field. All of the projects described in the breakout sessions were supported by the CBCRP. In these sessions, CBCRP-funded researchers gave oral presentations of their findings.

Services and Support for the Underserved

Breast cancer touches every California community, but the availability of treatment and support services varies widely. This session showcased researchers who are identifying and finding ways to overcome barriers to breast health services and information due to ethnic, racial, or geographical differences.

Sara O'Donnell, of the **Mendocino Cancer Resource Center,** and **Jeff Belkora, Ph.D.,** of the **University of California, San Francisco,** presented results of their research on promoting patient participation in treatment decisions in rural California. This is an example of the California Breast Cancer Research Program's Community Research Collaboration grants. These grants fund teams consisting of a trained academic research scientist and representatives of a community organization serving women impacted by breast cancer. This collaboration involved two cancer resource centers in two very rural counties, Mendocino and Humboldt. These counties have high poverty rates, many Native American reservations and rancherias, and a growing Latino population.

The research team tested an intervention called Consultation Planning, where a trained Consultation Planner meets with a woman recently diagnosed with breast cancer to help her list her top concerns. The Consultation Planner then creates a list of questions the woman can take to her appointment with her doctor where her treatment decisions will be made. This intervention had been researched and found to be effective when delivered face-to-face in an urban setting. Dr. Belkora's and Ms. O'Donnell's research team tailored the Consultation Planning process with input from local Latino and Native American cultural leaders and breast cancer survivors. Their research showed that Consultation Planning delivered by telephone is effective in a rural setting with Native American and Latina breast cancer patients.

A second Community Research Collaboration project presented here tested a breast cancer educational program for Samoans, with results described by **Seumaninoa Puaina, M.P.H.,** of the **National Office of Samoan Affairs,** and **Shiraz Mishra, Ph.D.,** of the **University of Maryland**. Samoans are Polynesian indigenous people from the U.S. territory of American Samoa, six islands in the South Pacific. Five more islands make up the independent nation of Samoa. Citizens of American Samoa are also U.S. citizens, but they don't have voting rights. Samoans have migrated to California in large numbers since World War II, with over 30,000 in southern California. Although data on breast cancer incidence among Samoans was difficult to find at the start of this research project, it appears that Samoan women have a breast cancer rate comparable to that of the group with the highest rate, white women. However, Samoan women in the U.S. have a lower rates of obtaining mammograms than any other ethnic group.

While it is widely believed that gaps between whites' and other ethnic groups' rates of having mammograms have narrowed, using more reliable data shows that minority women are 40-60 percent less likely than whites to have had one in the past two years.

The research team conducted a culturally-tailored education program delivered through 61 Samoan churches in Los Angeles and Orange counties. Since Samoan women did not identify with standard American Cancer Society booklets, the researchers created new booklets in Samoan and English. Samoan nurses facilitated four weekly educational sessions that ended with participants creating an action plan. The educational program increased mammogram screening among Samoan women who had never had a mammogram, and changed the level of knowledge in the community about breast cancer, but did not motivate women who had already had a mammogram to have another.

A third research project presented in this session addressed persistent racial and ethnic differences in breast cancer. African

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American women are less likely to get the disease, but more likely to die from it, than white women. There are fewer cases of breast cancer among Asians and Hispanics, but these groups don't have proportionately lower death rates. Most improvements in U.S. breast cancer death rates over the past decade have been among white women. **Rebecca Smith-Bindman, Ph.D.,** of the **University of California, San Francisco,** investigated some of the reasons behind these disparities. Based on self-report surveys, it is widely believed that gaps between whites' and other ethnic groups' rates of getting mammograms have narrowed, and that all groups are being screened with equal frequency. Using more reliable Medicare data, Dr. Smith-Bindman found that true rates of repeat mammography every two years are only about half of those from self-report surveys, and that minority women are 40–60 percent less likely than whites to have been screened within the past two years.

She also found that differences in mammogram rates for various ethnic groups are likely to contribute to—but not completely explain—differences in death rates. At diagnosis, African American women have higher rates than white women of three markers of tumors that are more likely to be deadly: larger size, later stage, and cancer in the lymph nodes. However, if African American women and white women who had mammograms at the same intervals are compared, these differences disappear. Mammograms don't make any difference in another marker that leads to higher death rates, tumor aggressiveness, and African American women have higher rates of aggressive tumors than other groups. While some of the breast cancer disparities among racial/ethnic groups are due to differences in type of tumor and treatment, Dr. Smith-Bindman concluded that equalizing access to mammograms would eliminate some of the difference in death rates, not only for African Americans, but also for Asians and Hispanics. Ongoing efforts are still needed to assure that minority and other underserved women have equal access to mammogram screening.

Emerging Topics in Breast Cancer Biology

The breast contains a variety of types of cells, each with its own job. By investigating how these different types of cells influence each other's behavior, and change as cancer develops, scientists should be able to intervene in the process.

Each cell's nucleus contains DNA, composed of genes arranged in long structures called chromosomes. Genes produce RNA, which, in turn, creates the proteins that carry out the functions of cells. Normal breast cells, and human cells in general, have 23 chromosomes. As cells become cancerous, their DNA becomes defective. Cells can lose entire chromosomes, and gain extra copies of others. When the cells have extra copies of genes, those genes lead to the cells producing more than normal amounts of some proteins. This is called amplification or overexpression of those genes. Genes that are amplified in breast cancer cells (oncogenes) are good targets for therapy, because the cells often cannot survive as cancer (or at all) without the proteins these genes produce.

Breast cancer cells can be divided into five subtypes, using their genetic profiles on microarrays. Each subtype has a different pattern of DNA gain and loss. This suggests that the different types arise through different sets of genes.

Kristiina Vuori, M.D., Ph.D., of **The Burnham Institute for Medical Research,** investigates breast epithelial cells (the cells where most breast cancer develops), in the context of chemical signals they receive from nearby cells called stromal cells. Her lab is studying a gene, DOCK180, that gets normal epithelial cells to move in response to chemical signals from the outside. If DOCK180 is overexpressed, it moves cells without outside signals, and it appears to drive the process of cancer cells moving to other body parts. DOCK180 is a good target for therapy. However, only one out of 5,000 targets yields results as a drug. The drug development process takes 12 to 15 years and costs $500 million. Dr. Vuori's lab is trying to develop a way to make the discovery process more efficient by improving the odds.

Candidate therapies are generally tested in breast cancer cell lines grown in a single layer. However, a tumor is three-dimensional. Dr. Vuori's research team developed a method for culturing breast cancer cells in a spheroid. They tested the drug rapamycin, which is used to treat kidney cancer, on breast cancer cells. It worked against cells grown in a spheroid, but not against the same cells grown in a single layer. Next, they tried

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radiation and low-dose rapamycin against the spheroid cultures. Alone, neither treatment stopped the cells from growing. Together, they stopped the cells grown in spheroid cultures, but not those growing in a single layer. The cells in the middle of the spheroid are under metabolic stress because they lack nutrients. Rapamycin blocks a protein that keeps cells under stress from digesting themselves. So rapamycin drives the inner cells in the spheroid to eat themselves, while radiation destroys the outer cells. The middle cells in the spheroid are under stress similar to tumor cells before the tumor has developed its own blood supply (angiogenesis), so rapamycin/radiation treatment would have more success before angiogenesis takes place. Dr. Vuori expects that using spheroid culture systems will better mimic the complex nature of chemical signals that pass between breast cancer cells and their environment, and possibly speed the development of new drugs.

A tool that can speed the search for therapy targets is the microarray. In the past, researchers worked inefficiently, finding one oncogene at a time. With microarrays, researchers can look at all 25,000 genes in a cell at once, and find those that are amplified. Using microarrays, **Jonathan Pollack, M.D., Ph.D.,** of **Stanford University,** has created a list of amplified genes in breast cancer cells. Some are known oncogenes, others are strong candidate oncogenes. He found two genes that neighbor a known oncogene, ERBB2 (HER-2). These neighboring genes are only amplified when ERBB2 is also amplified, and appear to support the action of ERBB2. This suggests it would be useful to target the neighboring oncogenes along with ERBB2, and that this might be effective for women whose tumors don't shrink in response to the available medication that blocks ERBB2, Herceptin.

Using their genetic profiles on microarrays, breast cancer cells can be divided into five subtypes, each with a different pattern of DNA gain and loss. This suggests that the different types arise through different sets of genes. Dr. Pollack's research team found a small region of genes that have not previously been identified with breast cancer. These genes are amplified on all breast tumors belonging to the subtype with the worst prognosis. One of these genes, CAMK, when overexpressed experimentally in normal cells, makes the cells lose contact with each other and become invasive. CAMK appears to be important to breast cancer spreading to other body parts, and could be a target for therapies in tumors with a poor prognosis.

Another emerging topic in breast cancer biology is breast stem cells. **Steven Artandi, Ph.D.,** of **Stanford University,** presented research he has conducted on changes in chromosomes in these cells that may be significant in breast cancer. Telomeres are protective caps on the ends of chromosomes, composed of repeated sequences of DNA bound by a protein complex. If cells don't have enough of an enzyme called telomerase, telomeres get shorter each time the cell divides, eventually leading to the cell stopping growth or dying. If telomerase is overexpressed experimentally in normal cells, the cells keep dividing and become immortal. Telomerase is overexpresssed in almost all breast tumors.

Dr. Artandi's lab bred "knockout mice"—mice lacking the ability to synthesize telomerase—for five and six generations. These mice had short telomeres. They developed mammary tumors with widely aberrant genomes similar to those seen in human breast cancer. This showed that short telomeres appear to facilitate tumor initiation. Further experiments, however, showed that short telomeres do not facilitate tumors spreading to other body parts, but instead keep a tumor from progressing.

In the fifth generation knockout mice, mammary gland development was also impaired. Mammary glands contain progenitor cells (stem cells) that have the ability to form all the cells in the gland. In a young mouse whose mammary gland has been removed, transplanting a small amount of mammary tissue from a normal mouse will regenerate the mammary gland. The stem cells start the regeneration. However, this doesn't work with mammary tissue from the fifth generation knockout mice. Telomere shortening appears to block the ability of stem cells to give rise to new stem cells, and probably impairs the ability of breast cancer cells to proliferate. This is why, as breast cancer progresses, telomerase gets reactivated and produces longer telomeres. These findings suggest that telomere shortening, which leads to unstable chromosomes, develops in breast stem cells.

Exploring Breast Cancer Risk

Understanding the risks associated with developing breast cancer may lead toward effective preventive strategies. Research has uncovered ways to predict rates of breast cancer in groups of women, but we still don't have ways to predict an individu-

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al woman's risk. **Karla Kerlikowske, M.S., M.D.,** of the **University of California, San Francisco,** discussed one important risk factor for breast cancer, breast density. Density refers to how breast tissues look on a mammogram. Dense tissues appear white; fat appears black. Dense areas seem to be composed of collagen and two types of cells, epithelial and stromal. Breast density is measured on a scale from 1 (fatty) to 4 (dense). A woman in category 4 has a 3.5 times greater risk of getting breast cancer than a woman in category 1. However, the scale is not very useful, because over 80 percent of women fall into the middle categories, 2 and 3.

Density goes down with age and drops at menopause. Hormone medications increase breast density, and the drug tamoxifen, which blocks the hormone estrogen, reduces breast density. All this suggests that hormones produced by the body may be involved in density. However, density is not related to levels of a number of hormones that circulate in the blood. Density is also associated both with tumors that depend on estrogen (ER+) and those that do not (ER-). Studies of twins suggest that a gene that can be inherited controls density, and women with a family history of breast cancer have higher breast density.

Current methods of measuring breast density are difficult for physicians to use and don't provide much information. Dr. Kerlikowske is involved in the development of a better method that will measure dense volume as part of a digital mammogram. The method doesn't interfere with interpreting the mammogram, and requires no additional radiation to the woman. Dr. Kerlikowske hopes that in the near future, this method can be used as part of a risk model to more accurately predict an individual woman's five-year risk for breast cancer. This would help women decide whether to use current preventive methods, such as taking tamoxifen, that have side effects.

How is a woman's risk for breast cancer affected by environmental exposures? Research is a long way from answering that question. One development that would help is an accurate method for testing which chemicals a breast has been exposed to. **Christopher Benz, M.D.,** of the **Buck Institute of Aging Research,** presented progress his team has made toward such a test. Studies in animals have identified 216 chemicals associated with mammary tumors, but these studies have questionable relevance for human breast cancer. Many of these chemicals affect the body in similar ways. Dr. Benz's research is an attempt to define what is carcinogenic about these chemicals.

The estrogen receptor (ER) is a protein composed of 595 amino acids that chemically binds with the hormone estrogen. Breast tumors are classified as ER+ if they make more than normal amounts of ER, which triggers chemical changes in cells that lead to cancer. ER+ breast cancer is the most common type in U.S. women over 40. It is also the most variable worldwide. Areas of the world with low breast cancer rates have lower rates of ER+ tumors than the U.S, but similar rates of ER- tumors. Estrogenic chemicals—from the environment or made within a woman's body—can cause cells to produce excess ER. Dr. Benz's hypothesis is that by understanding chemical modifications in the ER taken from breast tumors, we can find a chemical signature that shows what the ER has been exposed to.

A better measure of breast density could be used to more accurately predict a woman's five-year risk of breast cancer. This would help women decide whether to use current preventive methods, such as taking tamoxifen, that have side effects.

Dr. Benz's research team used mass spectrometry to measure chemical changes in the ER. Mass spectrometry, a faster technique than previous methods, can show changes in just one atom on a complex molecule. Their results showed that tumors classified as ER+ have varying amounts of ER that has undergone a chemical reaction called oxidation on a particular structure of the molecule. This chemical change had not previously been discovered, and it may allow the ER to get stuck in a mode where it triggers changes in the cell even in the absence of estrogen. This means that therapies that block estrogen would not necessarily be effective.

Since mass spectrometry is too expensive, and requires too many cells, to be used to test individual tumors, Dr. Benz's team created an antibody that can reveal the presence of two chemical modifications to the ER. This antibody test could be applied to small tissue samples like those used to test tumors for excess ER. This research illustrates the feasibility of inves-

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tigating chemical changes in the ER to find chemical signatures that will tell what a breast tumor was exposed to that perhaps led to the cancer.

Another factor that affects breast cancer risk is pregnancy and lactation. A pregnancy before age 24 protects against the disease. **Ameae Walker, Ph.D.,** of the **University of California, Riverside,** suggested that a form of the hormone prolactin plays an important role in this protective effect. During pregnancy and lactation, prolactin is released in large quantities by the pituitary gland. It enters the bloodstream, affects the portion of the breast that secretes milk, and promotes the synthesis of milk proteins. Prolactin receptors are proteins on cells that allow the cells to take up prolactin. It might be expected that these receptors on the epithelial cells that line the milk duct would primarily be on the outside of the duct, facing the blood supply, and not inside, facing the milk. However, in normal breast tissue, receptors are present all over, including the inside of the duct. During pregnancy and lactation, the ducts change so that almost all the receptors are on the inner surface of the duct, facing the milk.

Two types of prolactin are relevant here: the unmodified version, U prolactin, and a version that has undergone a chemical reaction called phosphorylation, P prolactin. From 70 to 100 percent of prolactin in milk is P prolactin. Dr. Walker and her colleagues determined that P prolactin inhibits cell growth and division, whatever the stage of the development of the breast. P prolactin also inhibits the growth and division of breast cancer cells. U prolactin promotes cell growth and division. During lactation, when the level of P prolactin in milk is 100 times higher than that in the blood, epithelial cells take U prolactin from the blood, transform it into P prolactin, and release it into the milk. Since prolactin receptors are found inside the milk ducts, this raises the question of whether administering P prolactin—or even milk—inside the breast ducts could provide the same protection against breast cancer as pregnancy and lactation before age 24.

Improving Breast Cancer Diagnosis and Therapy

The ultimate goal for breast cancer treatment is to make it as non-toxic to normal cells as possible, while still efficiently killing tumor cells. The method for achieving this goal is to identify which tumors will respond to specific therapies and treat them accordingly. Presentations in this session described how researchers are learning to recognize tumor cells in the blood, identify which tumors will respond to specific treatments, and develop new therapies from natural products.

Some tumors do not spread outside the breast, and surgery alone would be enough to stop them. Some tumors release cells that circulate into the bloodstream. Developing a test for circulating tumor cells in the blood could help identify which tumors have the ability to spread, and would spare women whose tumors don't have the ability to spread the toxicity of chemotherapy. If the test can also provide information on the tumor's genetic abnormalities, it could help predict prognosis and identify effective treatment. **Stephanie Jeffrey, M.D.,** of **Stanford University,** described her research team's new approaches to detecting and characterizing tumor cells in blood. Her team has a working method to obtain a "molecular fingerprint" of tumor cells—with a large amount of information on the genetic abnormalities that make the cells different both from normal cells and other tumor cells. This method allows them to classify tumors by molecular subtype, and the classifications can be used in decisions about which treatment will be effective. They are studying cancer cells that circulate in the bloodstream because cells within one tumor are not genetically identical. For example, among tumors that do not produce abnormally large amounts of the HER-2 protein, 50 percent shed cells into the blood that do produce abnormal amounts of HER-2. The cells that get shed into the blood are likely to be the ones that allow the tumor to spread to other body parts.

Finding cancer cells that circulate in blood is a challenge. Even among women with a tumor that has spread to another part of the body, most have fewer than 100 cancer cells, and many have fewer than ten, in a blood sample that contains millions of other cells. The research team is using technologies that include antibodies, magnets, micro-fluidic chips, and lasers to isolate cancer cells from blood, without killing the cells, so the cells can be cultured. After testing their technology on blood samples to which they have added a known number of cancer cells, they are able to isolate and capture alive a high percentage of the cancer cells, and get a molecular fingerprint from small samples, down to a single cell.

A new discovery may provide a way to assure that the highly toxic chemotherapy medication Adriamycin, and other similar

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anthracycline-based drugs, will be administered only to women whose against whose tumors it will be effective, according to **Michael P. Press, M.D., Ph.D.,** of the **University of Southern California.** Until now, many more women have received this medication than necessary, because there has not been a way to pinpoint which tumors will respond. Every cell in the body has two copies of a gene called HER-2. Approximately 25 percent of breast tumors have many extra copies of this gene, and they are called HER-2-positive (HER-2+) tumors. Women with this type of tumor in the past who were treated only with surgery were less likely to survive than women whose tumors were HER-2-negative. The medication trastuzumab (trade name Herceptin) blocks the action of the extra HER-2 genes, and dramatically improves disease-free and total survival time in women who have HER-2+ tumors. A number of studies have shown that Adriamycin works only against HER-2+ tumors, and on only a fraction of those. However, in lab studies, Adriamycin does not interact with the HER-2 gene or the cell processes this gene initiates. Dr. Press's research team thought another gene might be involved. They found a gene located near the HER-2 gene called topoisomerase II-alpha (TOP2A). In some HER-2+ tumors, there are also many extra copies of the TOP2A gene. Adriamycin interrupts the cell processes initiated by TOP2A.

Only women whose tumors also had extra copies of the TOP2A gene received any benefit from Adriamycin therapy. Since just eight percent of breast tumors have extra copies of TOP2A genes, testing tumor samples for this marker could spare the other 92 percent from the toxicity of Adriamycin.

To test their hypothesis that extra TOP2A genes could be a marker showing that Adriamycin would work against a tumor, Dr. Press's research team analyzed tissue samples from of study of 3,000 women with HER-2+ tumors who were given various combinations of treatments. Only the women whose tumors also had extra copies of the TOP2A gene received any benefit from Adriamycin therapy. The 60 percent of the women whose tumors were HER-2+ with no extra TOP2A genes had better survival with treatment that included Herceptin, but not Adriamycin, than they did with a combination of both medications. Herceptin is generally less toxic than Adriamycin, and combining the two makes Adriamycin even more toxic. Since only eight percent of breast tumors have extra copies of TOP2A genes, testing tumor samples for this marker could spare the other 92 percent from the toxicity of Adriamycin.

Another avenue of research aimed at less toxic breast cancer treatment is herbs. **Michael J. Campbell, Ph.D.,** of the **University of California, San Francisco,** tested 69 herbs and two beetles identified in traditional Chinese medicine as having anti-cancer properties and being specific to the breast. Twenty-one of the 71, when made into teas, killed breast tumor cells in lab cultures. Several more, when prepared as ethanol extracts rather than teas, were among the most effective against cancer cells.

The next step toward a chemotherapy agent would be to find and isolate the chemical compound in the herb that kills cancer cells. However, Dr. Campbell said that approach may miss other chemical compounds in the herb that help the cancer-killing substance do its work. These other substances may act by affecting another body system, such as the immune system. Or they may work to make the cancer-killing substance more potent. To evaluate herbs—and combinations of herbs traditionally prescribed to treat breast cancer in Chinese medicine—Dr. Campbell is using the tools of systems biology. In systems biology, the researcher analyzes an herb on the molecular, cellular, tissue, and whole plant levels. The same type of analysis is also done on the disease: it's molecular profile, and its effects on cells, tissues, and on all the body's systems. The researcher then compares the systems profiles of herb and disease. This approach is based on the theory that a woman with a breast tumor may also have associated problems with other body systems, such as the immune system. The goal is combinations of herbal therapies, tested with the scientific rigor of Western medicine—that target not only the tumor, but also help with other body systems involved in the cancer process.

Advances from CBCRP-funded Research

Poster Presentations of CBCRP-funded Research

Illustrated posters depicting the results of 80 research projects funded by the California Breast Cancer Research Program (CBCRP) were on display throughout the symposium. Our funded researchers were invited to display posters of their recently-completed and ongoing projects. They were on hand for a poster viewing session where they could answer questions and receive comments about their research directly from the public. Trained advocates were also available to interpret posters for non-scientist attendees. In addition, the symposium booklet given to all attendees contained abstracts of all research projects presented on posters.

Cornelius L. Hopper Award Winners

The Cornelius L. Hopper Poster Awards acknowledge investigators whose posters illustrating their research projects excel in three areas highly valued by the CBCRP: potential impact on breast cancer; research innovation; and best presentation to a lay audience. The awards take their name from Cornelius Hopper, who played a leading role in founding the CBCRP. The CBCRP's advisory Breast Cancer Research Council, whose backgrounds reflect the diverse makeup of the symposium audience, selected the poster award winners. The winners are:

Highest Potential Impact on Breast Cancer
Identifying Targeted Treatments for Wound-like Breast Cancers
Howard Chang
Stanford University

Most Innovative Research
Cost-effectiveness of Breast MRI Screening by Cancer Risk
Allison W. Kurian
Stanford University School of Medicine

Best Presentation to a Lay Audience
Identifying Metastatic Breast Cells from Peripheral Blood
Kristin Kulp
Lawrence Livermore National Laboratory

Con Hopper

Advances from CBCRP-funded Research

Poster Discussion of CBCRP-funded Research

In this plenary session, five researchers representing the high quality of CBCRP-funded research discussed their findings.

Obesity Lowering Breast Cancer Risk? Yes, but . . .

Weight gain and obesity lower a woman's risk for some types of breast cancer before she reaches menopause. However, until **Esther John, Ph.D.,** and her colleagues at the **Northern California Cancer Center** conducted their study, "Body Size and Premenopausal Breast Cancer Risk in a Multiethnic Population," it was unclear whether this was only true for white women, because little research had been done on other ethnic groups. Dr. John found that among Hispanic, African American, and white women under age 35, the heaviest had a 40 percent lower risk of breast cancer than the leanest, but only for tumors that that depend on the hormones estrogen and progesterone to grow (ER+ PR+ tumors). The patterns were similar for all three ethnic groups. On the other hand, the tallest women had a 77 percent higher breast cancer risk than the shortest. Despite the protective effects of obesity at young ages, it should not be considered a breast cancer prevention method. Obesity makes both pre- and post-menopausal women less likely to survive the disease, and raises a woman's breast cancer risk after menopause. The take-home message: Be physically active and eat moderately.

Diabetes Raises Breast Cancer Risk in Asian Americans

Diabetes appears to raise the risk of breast cancer. But being overweight also increases the risk of both breast cancer and diabetes. Is diabetes itself causing breast cancer, or does the increased risk of both diseases result independently from weight gain? **Anna H. Wu, Ph.D.,** of the **University of Southern California,** conducted a study that sheds light on this question. She compared over 1,000 Chinese American, Filipino American, and Japanese American women with breast cancer to a similar number of women without the disease, matched for age, ethnicity, and neighborhood of residence. Having diabetes raised these women's breast cancer risk, especially for the thinnest women. If a woman was overweight, diabetes only raised her breast cancer risk slightly more. These findings support the hypothesis that diabetes itself plays a role in the development of breast cancer. Measurements of sex hormones from women in the study provide evidence that diabetes plays this role in two distinct ways, by affecting both hormones and insulin.

Toward a Blood Test for Metastasis

Surviving breast cancer depends on timely diagnosis and treatment of metastases (tumors that spread to other parts of the body). Since breast tumors shed cells into blood, it is possible that detecting and classifying these cells can show if there is a risk for a future tumor. No current test can do this. **Kristin Kulp, Ph.D.,** and her colleagues at **Lawrence Livermore National Laboratory** are making progress toward a blood test for breast cancer metastasis using a technology called Time of Flight Secondary Ion Mass Spectrometry. This technology can provide a "spectra fingerprint" of ions in a cell to identify the cell type. One challenge is to capture 10–100 cancer cells from millions of cells in a blood sample. After finding commercially-available capture methods inadequate, the research team has combined some of these methods with methods of their own. They now have a way to both capture and test the cells that can differentiate two types of breast cancer cells that metastasize from one type that doesn't. The goal is to develop spectra fingerprints for 60 breast cancer cell lines that will allow them to determine, in a process that takes less than an hour, whether isolated cells have the potential to metastasize.

Treatment for High-Risk Breast Cancer

The body's mechanisms for healing wounds are remarkably similar to the processes that allow breast tumors to spread to other body parts. **Howard Chang, M.D., Ph.D.,** of **Stanford University,** discovered that 30–40 percent of breast tumors have wound-like features, and having a wound-like tumor triples a woman's risk of death. The research team found a pattern of 512 genes that characterize wound-like breast cancer. Mapping the activity of these genes allowed the team to generate several ideas for targets for therapy that could block processes that allow these cells to survive. One commercially-available drug, bortezomib, blocks wound-like breast cancer cells in lab cultures. Although bortezomib has not worked

Poster Discussion of CBCRP-funded Research

against breast cancer in the past, it may work against wound-like tumors. The research team is working on a diagnostic test for wound-like tumors and exploring additional possibilities for treatments.

Even Pre-Malignant Cells Create Their Own Blood Supply

Breast cancer arising in the milk ducts is believed to progress in stages. Starting from the normal breast, the first stage is hyperplasia, a benign increase of duct cells. Next is atypical hyperplasia, with pre-malignant duct cells. Next is ductal carcinoma in situ (DCIS), with cancer cells confined to the duct. With infiltrating ductal carcinoma, the tumor has invaded the duct wall. Somewhere along the line, the tumor must stimulate the growth of new blood vessels in order to grow and survive, a process called angiogenesis. It has been believed that angiogenesis occurred fairly late in the progression, but **Philip M. Carpenter, Ph.D.,** and colleagues at the **University of California, Irvine,** found evidence that angiogenesis is already ongoing, to a small extent, during hyperplasia, and that it increases during each stage. This research points to the possibility of treating DCIS with existing treatments that block angiogenesis, and explains why hyperplasia is sometimes detected by magnetic resonance imaging (MRI).

A Unique Scientific Meeting

Sharing experiences and ideas—between women coping with breast cancer, research scientists, breast cancer advocates, healthcare professionals, social service professionals, and community organizations serving women impacted by the disease—was the hallmark of the CBCRP's fifth symposium.

At a Meet the Experts Breakfast, the public discussed breast cancer topics in small groups with research scientists and other experts. Topics ranged from advocacy for young women with breast cancer, to new drug development for treatment, to the environment and breast cancer. Attendees new to breast cancer could get the basics at a workshop called Breast Cancer 101, led by M. Ellen Mahoney, M.D., F.A.C.S., of the Community Breast Health Project.

Our symposium included a workshop for researchers who wanted to learn to navigate our process for applying for a research grant. We also provided an extra day of training for members of community organizations and experienced researchers interested in teaming up to conduct research with funding from the CBCRP's Community Research Collaboration awards.

Representatives from California community organizations staffed over 20 exhibits. They provided information about what women could do for themselves and their communities to reduce the impact of breast cancer, including reducing their risk of getting the disease, finding support groups, and joining advocacy efforts to advance policy changes that improve access to diagnostic services and care.

CBCRP Listens, a town-hall-style meeting, invited feedback on our Special Research Initiatives, which will investigate the role of the environment in breast cancer and the reasons why some groups of women bear a greater burden of the disease than others. We take this feedback from the public seriously. At past CBCRP Listens sessions, participants asked, "Why don't you do more research on cancer and the environment?" This feedback is one factor that led to our setting aside 30 percent of our funds over five years for the Special Research Initiatives. This year, participants had the opportunity to give feedback on ideas submitted for research to be conducted through this effort.

A few days after our symposium ended, we invited all participants to give us feedback on it via email. We also invite you to become part of this conversation. You can access symposium research abstracts and slide presentations, listen to a plenary presentation, and give us your own feedback at our website (www.CABreastCancer.org). We also invite you to contact us directly or participate in our research efforts.

Healthy and Environmentally Friendly

The CBCRP designed our statewide symposium to be not only informative, but also healthy and environmentally friendly. We took measures that included offering free yoga and exercise classes each morning, serving organic produce when possible, reducing the use of plastic products and eliminating the use of Styrofoam products in our food service, producing all symposium materials on recycled chlorine-free paper with soy-based ink, and providing opportunities for recycling.

Science Meets Art at the CBCRP Symposium

To bring into focus the reason behind our urgent work toward better methods to treat, cure, and prevent breast cancer, the CBCRP's symposium includes a curated biennial art exhibition. This year's exhibition wove together a diversity of experiences that reflected the far-reaching impact of this disease. Works included painting, photography, sculpture, graphic art, textile art, and mixed media. Also on view was *Expressions: the Art of Science and Healing,* the CBCRP's collection of wearable breast art, which has been shown in California art galleries. The art ranged from the political to the personal, from the celebration of life to the processing of profound loss. Some participants were seasoned, award-winning artists, while others had newly discovered the transformative power of art, employing it as a vehicle for healing and growth. Each unique perspective embodied vision and courage. These works of art represented a much larger chorus of voices who underscore the importance of advancing our understanding of breast cancer.

About the California Breast Cancer Research Program

- The mission of the CBCRP is to eliminate breast cancer by leading innovation in research, communication, and collaboration in the California scientific and lay communities.
- One of the top-rated research funders in the nation, the CBCRP is administered by the University of California, Office of the President.
- The CBCRP is funded through a portion of the tobacco tax, voluntary check-off contributions made on state income tax returns, and individual contributions.
- Since 1993, contributions to the CBCRP via state income tax returns have totaled over $5 million.
- Ninety-five percent of our revenue goes directly to funding research and education efforts. This revenue is used to make grants for California scientists and community researchers to find better ways to prevent, treat, and cure breast cancer.
- Since 1994, the CBCRP has awarded over $181 million for 761 grants to 92 California research institutions and community organizations.
- The CBCRP supports innovative breast cancer research—like cow viruses, Tibetan herbs, snake venom—that might otherwise go unfunded. With continued investment, the CBCRP will work toward a future without breast cancer.

2006-2007 Breast Cancer Research Council

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