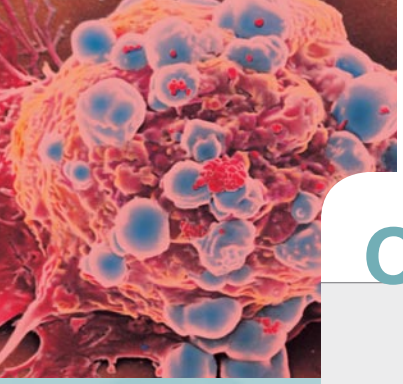


UCSF Helen Diller Family Comprehensive Cancer Center

cancer report

university of california, san francisco

volume 10.1
winter 2008

Breast Density and a Better Cancer Risk Model

Recent research indicates that having dense breasts is the biggest breast cancer risk, apart from normal aging or having two or more of one's closest relatives – mother, sisters – diagnosed with the disease. About one in three postmenopausal women has dense breasts.

But how does a woman know whether she has dense breasts? And if she does, what is she supposed to do with this new knowledge?

UCSF researcher Karla Kerlikowske, MD, is working with physicist John Shepherd, PhD, and Steven Cummings, MD, to develop a better way to measure breast density. She also is creating new, simpler models for tallying breast cancer risk. These models include breast density as one risk factor among several.

Thea Tlsty, PhD

There are drugs – Nolvadex and Evista – approved as preventive treatment by the US Food and Drug Administration for women scored as high risk on an index called the Gail model. But in practice, Kerlikowske says, few physicians are comfortable using this model as the basis for recommending drug treatment or more intense cancer screening, and few women actually take the drugs for prevention.

Working toward a risk model that physicians will trust and use more, Kerlikowske and Jeffrey Tice, MD, have come up with a first-generation prototype. Their new model considers only breast density, age, ethnicity, and whether a woman has had any breast biopsies or a mother or sister with a breast cancer diagnosis. "It's definitely better than the Gail model, and it's a lot simpler," Kerlikowske says.

What Are Dense Breasts?

Dense breasts are the opposite of fatty breasts. They have a higher proportion of connective and milk duct tissue. Breast density does not appear to relate to breast size or shape. It decreases with age and after menopause.

(continued on page 2)

CONTENTS

UCSF Renames Cancer Center

The UCSF Comprehensive Cancer Center has been renamed as a tribute to San Francisco native Helen Diller and her family. All UCSF cancer programs and resources will now carry the Helen Diller Family Comprehensive Cancer Center name.

The new name honors Diller for her commitment to improving lives around the world and for serving as a role model who inspires others to make a difference in their communities.

"Helen Diller believes that inspiring education and scientific discovery can help transform the world, and this is evident in her philosophy and practice. In recognition of her life and accomplishments,

(continued on page 8)

Saving Language in Brain Cancer Patients

For patients with deadly brain cancers called high-grade gliomas, preserving language is of paramount importance. Few outlive these cancers, but many live pain-free for a year or longer.

"The loss of language function during a patient's battle against brain cancer is a devastating blow and significantly compromises quality of life," says Nader Sanai, MD, a senior neurological surgery resident at UCSF. Sanai, along with his mentor, department Chair Mitchel S. Berger, MD, has a special interest in mapping language function in order to preserve it during surgery.

A decade ago, Berger emerged as a pioneer in functional brain mapping of glioma patients. Now Berger, Sanai and a UCSF colleague have published new clinical research findings in the January 3, 2008, issue of the *New England Journal of Medicine.* The findings may change the standards for language mapping during tumor removal.

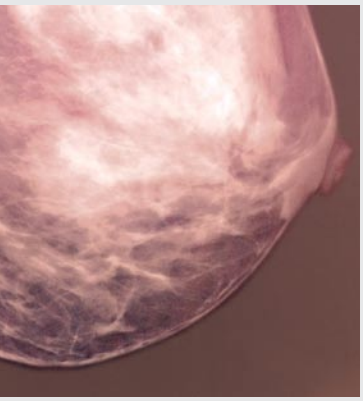
Surgeons previously relied on a method called "positive language mapping." But in a new twist, the UCSF neurosurgeons report that a different strategy, "negative language mapping," may allow for shorter, less extensive surgeries and work just as well to save language and life quality.

Many brain cancer patients who come to UCSF are referred by physicians who recognize the importance of preserving language function, but who are not affiliated with hospitals where surgeons routinely perform language mapping in awake patients during surgery.

Positive and Negative Mapping

The point of positive language mapping is to keep looking for the location of language function until it is found – even if it requires removing a larger portion of the skull and exposing brain regions far from the tumor.

(Breast Density continued from front cover)



Digital mammogram shows opaque areas where breast tissue is dense.

Where the breast is dense, a mammogram of the tissue appears cloudy or opaque. Radiologists normally inspect mammograms and provide a qualitative assessment of density. In women with dense breasts, 50 percent or more of breast tissue appears opaque.

Women past menopause whose breast density is 75 percent or more have roughly three to four times the risk of being diagnosed with breast cancer within five years compared with women whose breast density is 25 percent or less, according to Kerlikowske's research.

X-rays are the basis for mammograms, but with different instrumentation, X-rays also are the basis for a technique used to measure bone density. The UCSF research team has modified this technique, shifting the focus from bone density to breast density measurement. Its use requires no radiation beyond what is needed for the mammogram, Kerlikowske says. Physicians now are using the new measure at six sites nationwide.

Biology of Breast Density and Cancer

Just knowing that breast density is associated with breast cancer risk does not reveal why. To get at the biology, UCSF cancer and cell biology researcher Thea Tlsty, PhD, is leading a major new study funded by the National Cancer Institute.

Tlsty earlier saw that the abundant connective tissue and collagen protein found in normal, dense breast tissue superficially resembles the abnormal proliferation of connective tissue that occurs in the vicinity of cells that have undergone early steps toward becoming cancerous.

Now, Tlsty is leading research to compare normal, dense breast tissue with abnormal, precancerous breast tissue in molecular detail. Her lab team is tracking which genes are switched on and off in the milk duct cells that can give rise to cancer. The researchers are doing the same with the fat or connective tissue cells that surround the ducts. These different cell types take directions from one another. Abnormal signaling between duct cells and surrounding cells is a hallmark of breast cancer, Tlsty and others have found.

Tlsty suggests that the genetic events, proteins and signals that govern whether certain immature cells in the breast become fat cells or connective tissue cells might also play a role in cancer susceptibility.

"It's very exciting, and we hope to have more to report soon," she says. •

Mitchel S. Berger, MD, and Nader Sanai, MD

Brain surgeons have regarded positive identification as the best method to ensure patient safety. The assumption has been that unless the critical function is found, it might remain undiscovered within the field of surgery and thereby be compromised unknowingly.

With negative language mapping, the neurosurgeon only probes close to the tumor to search for function. If the neurosurgeon does not locate any functionality, it is assumed to be outside the field of surgery. The advantage of negative language mapping is that it often is faster and less invasive, and lowers the risks associated with longer procedures.

The gliomas of the 250 patients in the UCSF study were often very large and in the most challenging locations. To negatively map language sites, Sanai and Berger exposed only the tumor and surrounding cortex. They searched only within about an inch (2.5 centimeters) of the tumor. The surgeons refrained from removing brain tissue within a centimeter of language sites – about a dime's diameter.

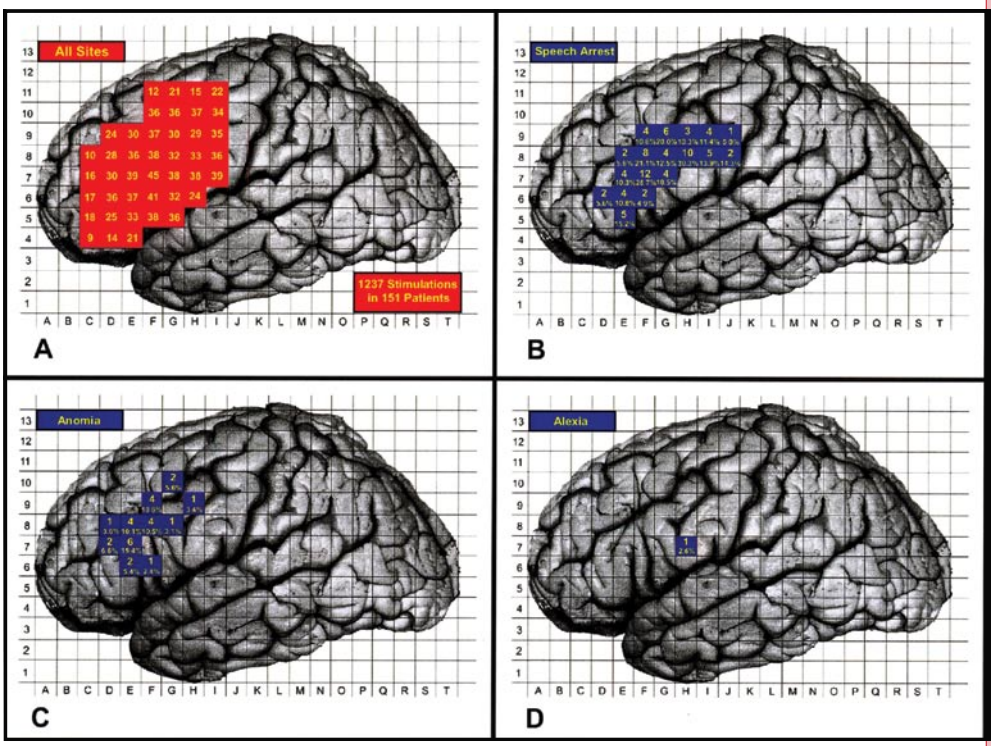
Importantly, compared with positive language mapping, negative language mapping posed no additional risk to language or life.

Variability of Language a Big Surprise

Many brain tumors arise in the vicinity of Broca's area, a neighborhood of the frontal lobe in the dominant brain hemisphere known to contain language function. Although brains are less variable in appearance than fingerprints, the folds and contours within the brain differ from person to person. Surgeons have long known that Broca's area does not map to a distinct anatomical location. That's why precise mapping during the operation is the gold standard.

But now someone may need to rewrite the text chapters on brain anatomy and function. The experience of the UCSF clinical research team has also revealed that it is not uncommon for language sites to be located surprisingly far from Broca's area – a paradigm-shifting discovery in brain research.

"Our experience reveals tremendous variability in language-site localization," Sanai says. "But based upon the thousands of cortical stimulations we've recorded in this study, we can finally generate an accurate, three-dimensional map of language function in the human brain." •



Neurosurgeons electrically stimulated brain sites to locate language function. Panel A shows the total number of stimulations of various square-centimeter-size regions in 151 patients. Panel B shows the number and sites of stimulations that caused speech arrest. Panel C shows stimulations that resulted in anomia, the inability to recall words. Panel D shows stimulations that resulted in alexia, the inability to comprehend written words.

Turning the Tide of Liver Cancer Among Asians

A largely preventable cancer is expected to become more common in the United States in coming years.

No, it's not lung cancer – the decades-long decline in smoking rates finally is leading to fewer lung cancer deaths in both men and women.

It's liver cancer.

"It's deadly and it's preventable," says UCSF investigator Tung Nguyen, MD.

The cause of more than eight in 10 liver cancers in the United States is chronic infection with the hepatitis B or hepatitis C virus. The number of new hepatitis infections is declining. But just as there has been a lag between the decline in smoking and the drop in lung cancers, it may take many years before the trend toward fewer hepatitis cases and better hepatitis treatments leads to fewer liver cancers. Liver cancers arise a few decades after infection, and a few decades ago, hepatitis infections were still on the rise.

Nguyen – who emigrated as a child from Vietnam – is fighting hepatitis in Bay Area Asian communities. Through outreach and training of key community members and through campaigns in ethnic media,

Tung Nguyen, MD

Nguyen and his collaborators aim to help reverse the US liver cancer trend as quickly as possible.

Hepatitis B Is Common

Why focus on Asians? Hepatitis B is common in many parts of the globe, including Asia. Because of this, liver cancer is the third most common cause of cancer death worldwide. Immigrants from Asian countries are infected at high rates. So too are their children. For instance, in San Fran-

Joel Palefsky, MD

Top: human papillomarvirus (HPV).

HPV Vaccine for Men?

The new vaccine used to prevent sexually transmitted human papillomavirus (HPV) in women and girls could play the same role in men and boys, says UCSF Professor of Medicine Joel Palefsky, MD. Without vaccination, Palefsky adds, "about 75 percent of men and women are going to get an HPV genital infection at some point."

In females, the vaccine, called Gardasil, prevents infection by two HPV strains that are responsible for 70 percent of cervical cancers. The vaccine also prevents infection by two strains that cause 90 percent of genital warts.

In 2006, Gardasil was licensed for use in girls as young as 9. The US Centers for Disease Control and Prevention recommends vaccination for girls starting at age 11 and for women up to the age of 26.

Merck, the maker of the vaccine, now is conducting a worldwide clinical trial in men and boys ages 16 to 26 with few or no lifetime sexual partners. Most have never been infected. As part of this trial, Palefsky will be studying a subset of males – young men who have had sex, or who expect to have sex, with other men.

Culprit in Cervical, Anal, Oral, Penile Cancers

In men and boys, the vaccine is expected to prevent common penile warts and about half of penile cancers, a rare disease. In addition, the vaccine is expected to prevent oral cancers due to HPV infection, the incidence of which is increasing, especially among men.

HPV infection also is the primary cause of anal cancer. In the United States, anal cancer incidence is increasing among both women and men. HPV infection rates are especially high among HIV-positive men and women, Palefsky notes, and the highest rates of HPV-associated cancers occur among men who have sex with men.

(continued on page 7)

UCSF Origin of Hepatitis B Vaccine

Beginning in the late 1970s, research by William J. Rutter, PhD, then the chair of the Department of Biochemistry and Biophysics at UCSF, laid the groundwork for modern hepatitis B vaccines. Rutter showed that an uncontaminated source of material for a hepatitis B vaccine could be obtained by mass-producing viral proteins in genetically engineered, laboratory-grown yeast. Rutter founded the biotech firm Chiron, which became the first company to market a genetically engineered hepatitis B vaccine.

cisco, where according to the 2000 census nearly one in three people is Asian, an estimated one in 10 Chinese is infected with hepatitis B.

Today in the United States, hepatitis C is mainly spread by IV drug users sharing needles, and there is not yet a commercially available vaccine. On the other hand, there are vaccines to prevent hepatitis B infection. The vaccine strategy originated with pioneering research at UCSF (see sidebar). Children in the United States now are routinely vaccinated early, before they mature and become sexually active.

But mothers can easily pass hepatitis B to their children in the womb. This is the major source of existing hepatitis infections in the US Asian community, Nguyen says. In addition, many children who immigrate to the United States miss school vaccinations and risk becoming infected later.

Infection is lifelong. Only a minority infected with hepatitis go on to develop liver cancer. But because so many in Asian communities already are infected at birth, Nguyen explains, some are developing liver cancer in their 30s or even in their 20s. Increasing liver cancer screening among people who test positive for hepatitis is an important outreach goal, Nguyen notes.

Disease Is Often Symptomless

Hepatitis often has no symptoms. “Some people get vaccinated without getting tested first to see if they already have been infected,” Nguyen says. “They think they are protected, when in reality they already may be infected, and infecting others.”

Nguyen is a partner in a San Francisco Department of Public Health program to combat hepatitis B. The aim of “San Francisco Hep B Free” is to screen, vaccinate and treat all Asians and Pacific Islanders who live in the city, in part by providing free or low-cost testing.

Nguyen also is a regional leader in the Asian American Network for Cancer Awareness, Research and Training, and he directs the Vietnamese Community Health Promotion Project. He heads up a new National Cancer Institute-funded educational campaign for Vietnamese in Bay Area counties, which targets the community with messages via radio, television, print publications and online media. Vietnamese in the United States have the highest rate of liver cancer, about 11 times higher than the rate among whites.

To get out the word, it’s best to use individuals who are esteemed in the community, ranging from physicians and local ethnic celebrities to socially connected and specially trained lay health workers who can be effective in persuading people to get screened, vaccinated or treated, Nguyen has found.

“It’s not just the message; it’s who’s delivering the message,” Nguyen says. •

Thyroid Cancer Cases Climb as Treatment Advances

Overall, cancer rates are declining in the United States, but some cancers are on the rise. Among these, thyroid cancer rates are climbing the fastest.

Diagnosed cases in the United States now number more than 30,000 each year. The population's risk for the disease doubled from 1974 to 2004, according to the National Cancer Institute. Each year, about 1,500 people now die as a result of thyroid cancer. Many more women than men are stricken.

Orlo Clark, MD

Scientists who study disease trends suspect that better detection may be responsible for much of the rapid rise in thyroid cancer diagnosis. Others point to radiation or other environmental threats. Some evidence also suggests that being overweight is associated with a higher risk of certain forms of thyroid cancer. The trend toward growing numbers of overweight people in the United States is decades-long.

Treatment Advances

Whatever the causes of thyroid cancer, physicians at UCSF aim to cure or at least control it with appropriate treatment. On the other hand, they want to avoid hormone imbalances, harm to vocal cords or other side effects that diminish quality of life.

Research shows that thyroid cancer patients fare best when treated by the most experienced surgeons – and the five endocrine surgeons who treat thyroid cancer at UCSF are among the most experienced.

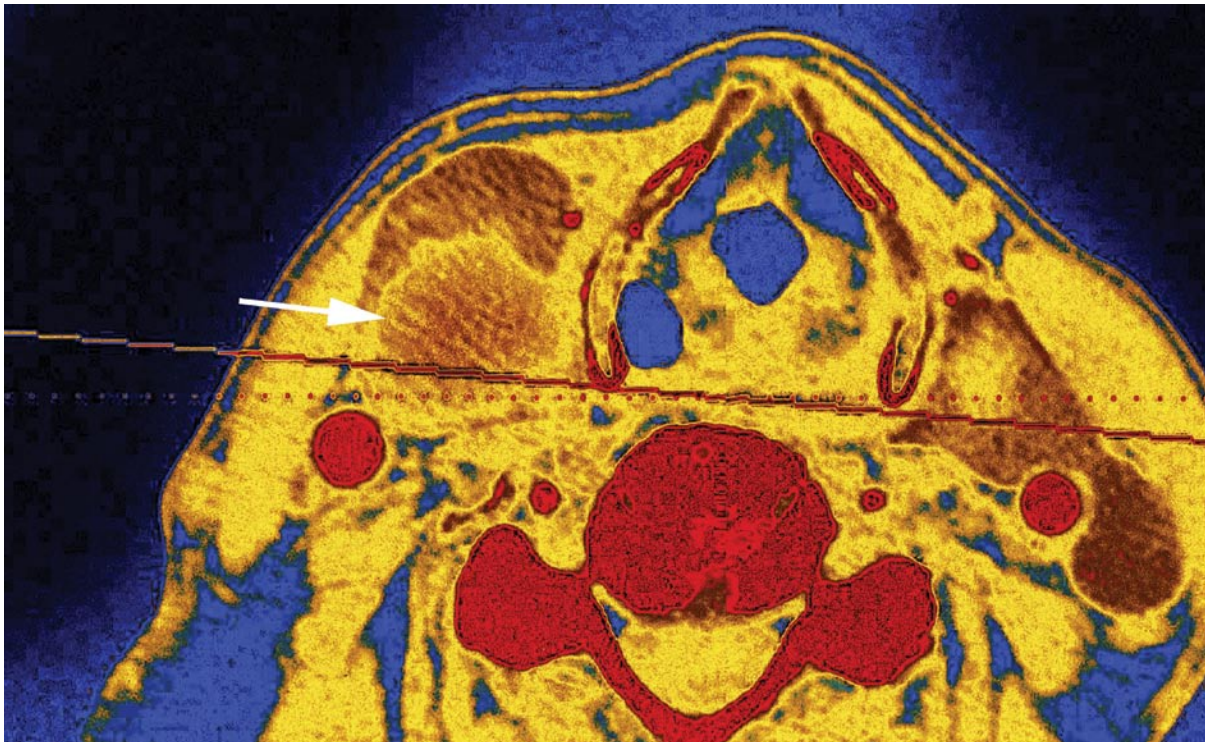
Orlo H. Clark, MD, former chief of surgery at UCSF Medical Center at Mount Zion, has been an early user of improved techniques and equipment throughout his 30-year career as a specialist in endocrine tumors. Early on, he created a stir by being among the first to advocate total removal of the thyroid in most cases of thyroid cancer. He justified the now generally accepted approach by showing that side effects of the surgery could be reduced, while at the same time cutting the chances of the cancer returning. Replacing thyroid hormone normally is not difficult.

Clark and his fellow UCSF endocrine surgeons also were among the first to save the function of the neighboring parathyroid gland during thyroidectomy – by transplanting a portion to the arm – in cases where the blood supply to the parathyroid was compromised. More recently, UCSF thyroid surgeons have become experts in minimally invasive and endoscopic procedures to remove thyroid and parathyroid tumors.

Search for Molecules That Predict Cancer Growth

The most common and curable form of thyroid cancer is called papillary thyroid cancer. It

CT scan showing a thyroid tumor.



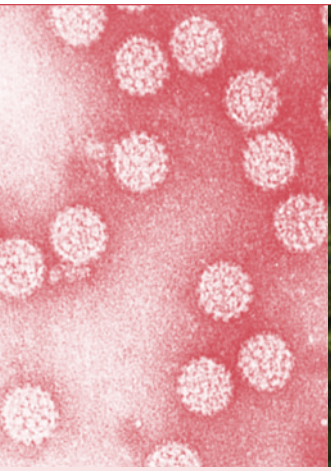
accounts for 80 percent of cases. About 7 percent of patients die of papillary thyroid cancer within 10 years of diagnosis. A less common form, medullary thyroid cancer, arises in a different part of the gland. It is about four times as deadly.

Unfortunately, growth of individual tumors or a recurrence of cancer after treatment is not always predicted by size, location or how cancer cells look to a pathologist. These factors are not much of a guide in deciding how aggressively to treat patients with thyroid cancer.

Clark notes that over the past decade, blood thyroid hormone markers, use of radioactive iodine, and improvement in ultrasound, CT, MRI and PET imaging have dramatically increased the detection of residual thyroid tumor tissue in lymph nodes and elsewhere following surgery. In many cases, this detectable tumor tissue does not grow aggressively.

Clark and surgeons Electron Kebebew, MD, Quan-Yang Duh, MD, Wen T. Shen, MD, and Jessica Gosnell, MD, are leading efforts to identify molecular markers in biopsy tissue. These markers should help distinguish aggressive cancer – requiring additional surgery, radiation or chemotherapy – from tumor tissue that only requires monitoring because the markers indicate it is unlikely to grow in a threatening way.

"Our job is to think of new ways of doing it better," Clark says. •



(HPV Vaccine continued from page 4)

Earlier studies showed that boys and girls mount similar immune responses to Gardasil. But the new phase III clinical trial is the true test of whether the vaccine prevents HPV infection in males. Even so, male vaccination already is approved in some other countries.

"If the vaccine is effective in males, then for men who have sex with men, it will be beneficial," Palefsky says.

Cost Versus Benefit Is an Open Question

For other males, lowering risks for rare or minor diseases through vaccination may or may not be worth the cost, Palefsky says. Despite its lifesaving potential, some say Gardasil has not been studied long enough to know much about side effects. Its high price also is an issue – about $360 for three doses – as is its failure to protect against all disease-causing HPV strains.

Another consideration is that if not all girls get the three recommended doses, then vaccination of boys could help increase collective "herd immunity," further lowering HPV transmission and, ultimately, cervical cancer incidence.

"These are good things, but we would still need to look closely at the costs and benefits of vaccination," Palefsky says.

If there is no recommendation that all boys be vaccinated, then those most at risk may lose out, Palefsky says. "There are likely to be many young people who have identified themselves as gay, but who have not acted on it yet. They are unlikely to go to a school nurse, say they are at risk and ask to be vaccinated." •

Cancer Report
Volume 10, Number 1
Winter 2008

An information resource for UCSF Helen Diller Family Comprehensive Cancer Center supporters, advocates, patients and caregivers.

Cancer Report is published by the UCSF Helen Diller Family Comprehensive Cancer Center at the University of California, San Francisco.

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Produced by University Publications/Public Affairs, PR706

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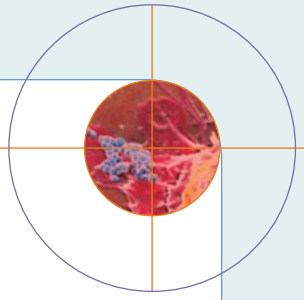


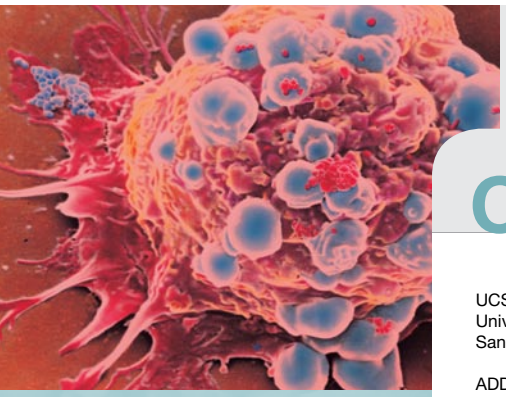
(Cancer Center Renamed continued from front cover)

we are pleased to rename the cancer center in her honor," said UCSF Chancellor J. Michael Bishop, MD. "The UCSF Helen Diller Family Comprehensive Cancer Center works at the leading edge in all areas of cancer research and patient care, and the new name will be synonymous with this new era of cancer discovery."

The Helen Diller Family Comprehensive Cancer Center will help UCSF build on an established track record of cancer innovation. In the coming years, the Helen Diller Family Comprehensive Cancer Center will work to accelerate the pace at which research findings are translated into lifesaving tools to diagnose, treat and prevent cancer.

"This is a tremendous honor for me and my family, and I am proud to have my name associated with one of the leading health care institutions in the country," said Diller. "I know that the thousands of patients who come here will benefit from the expertise and care that is a trademark of UCSF, and discoveries made here also will benefit scientists, clinicians and patients around the world. It is thrilling to think about the potential global impact on quality of life."

A resident of San Mateo County, Diller has a history of philanthropic giving to education, science and the arts. She is recognized for her creativity in looking for opportunities to contribute and for her deep involvement in the areas she supports. She created the Helen Diller Family Foundation nearly 10 years ago, and its gifts have supported a number of programs and institutions in the Bay Area and throughout the world. •



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