

Tips for communicators

Know your audience to pick the best strategy

Building a base of information about potential environmental causes of breast cancer is only part of the path toward a reduction of the disease. Individuals have to act on those findings. At the 2005 conference on Emerging Topics in Breast Cancer and the Environment Research, two members of Michigan State University's Department of Communication provided an overview of strategies that could be used to educate target audiences about the possible association between a proper diet in girls and a lower, future, breast-cancer risk, and to influence girls to eat better.

"You can aim messages directly at the girl, or indirectly at the mother or father, who then relays the content and influences the girl," said Charles Atkin, Ph.D. Another option is to level messages at policy-makers, who determine the food opportunities for communities or societies as a whole. The methods to reach each of these target audiences vary, he said.

For girls and their parents, messages about girls' diets may be best-couched in relationship to outcomes other than health, Dr. Atkin said. "We find factors like the promise of better athletic performance, greater attractiveness and the impact on self esteem can be used to motivate girls to comply with the (dietary) recommendations, or to influence the parents to guide their children to healthier food choices."

Health-associated messages do, however, have their place. The connection between a child's diet and a possibly higher incidence of breast cancer 30, 40 or 50 years down the line is a tough sell to an adolescent, but could have an impact on parents, he said. These messages are most effective if also connected with more immediate implications, such as the link between obesity and diabetes.

Decreasing high-fat, low-nutrient foods, and increasing organic and other foods that confer cancer protection are important messages, but communicators should also remember to provide information about healthy food preparation, added co-speaker Maria Lapinski, Ph.D. This is especially important for target audiences who have only recently moved to this country, she said. "People who are new immigrants to the United States face a lot of stress and a lot of concerns around health and diet. One of these things, in particular, is the type of foods to which they have access and their ability to prepare them in a healthy fashion."

Another factor that may play into the choice of a communication strategy is the role of society on food-consumption habits, she said. "Food consumption in our culture is a very social event in many cases, and we know that our relationship with our social groups drives our eating patterns in a lot of cases." For example, she said, a person may feel embarrassment about poor food choices when he or she is around others. "We also know that people who are part of particular cultural groups living in the United States — in particular Hispanics and African Americans — tend to be more collective in their orientation, so the group force is even more powerful." Communicators should consider how to use these influences in their persuasive messages, she said.

Dr. Atkin outlined some of the best ways to reach girls and their mothers. For girls, television and the internet are good communication avenues. "TV spots have a lot of potential if you can get them on the air, and the networks and local stations are sometimes cooperative. because this is not a highly controversial type of subject." Another option is to approach entertainment programmers about inserting educational

information into the scripts of movies and TV shows, he said. "Games and internet sites also work well for girls, as do printed materials, whether they are posters, comic books and even things are to them via direct mail."

Feature articles in magazines, newspapers, other printed materials, and the internet are effective tools for reaching mothers, he said. According to MSU studies, women respond to information from major cancer organizations, medical centers, foundations and universities. However, he state

Stone-age genes, space-age times Studies tie increasing weight among girls to earlier puberty, possible cancer risk

Fifteen thousand years ago, humans were hunter-gatherers who consumed little if anything when food was scarce, but ate heartily and stored energy as body fat when they had a chance. Their genetic makeup was well-suited to that up-and-down lifestyle. "Our genes haven't changed. We still have the stone-age genes, but we live in space-age times. If we want to gather an extra 5,000 calories, all we have to do is go down and order a couple of super-sized meals," said Frank Biro, M.D., Cincinnati Children's Hospital Medical Center. "At no time in human existence have people been able to purchase so many calories for so little relative money."

This comparatively high standard of living is having several unfavorable consequences, including an increase in the weight of children and teens, said Dr. Biro, who presented a session called "Influence of Obesity on Timing of Puberty" at the 2005 conference on Emerging Topics in Breast Cancer and the Environment Research. He pointed out numerous studies that have linked increased weight in girls with earlier onset of puberty and menstruation, and possibly with a higher future risk for breast cancer.

For example, research has documented a dramatic hike in the overall size of Americans, as measured by the body mass index (weight in kilograms divided by height in meters squared). A person with a body mass index, or BMI, of 25 is considered overweight, and a BMI of 30 falls into the obese category. "There has been an increase of about 50 percent in those exceeding a BMI of 25 over the span of 1980-1997, and almost a tripling of those with a BMI greater than 30," Dr. Biro said. "Among girls who are in early puberty, the rate of an elevated BMI, which is a risk for overweight, has gone from a little more than 3 percent to almost 15 percent over these years." He added, "We now see a fair number of 250-pound, 13- and 14-year-old girls, and that's something we really hadn't seen when I started practicing in Cincinnati 22 years ago."

The reason for larger-sized children is the combination of more calories and less exercise, he said. A 2001 study comparing diet of 6-11 year olds over a 30-year period showed that they were eating 150-200 calories more per day, and that snacks were making up a greater portion —18-24 percent more — of their daily diets, he recounted.

In 2004, another study found that teens ate fast foods on 30 percent of days. Biro remarked, "They are eating more fast food and fewer meals at home. The things they consume at fast-food restaurants are typically very calorically dense and contain a greater percentage of saturated fat, and they are much more likely to be consuming soft drinks instead of milk."

At the same time that girls are eating calorie-rich diets, they are exercising less, he said. Researchers in a 2002 study tracked exercise levels in females from the time they were 9-10 years old to their 18th or 19th years. "Regular, organized physical activity decreased by 100 percent in African-American girls, and by about 55 percent in white girls," he said.

The resulting increases in weight can lead to early pubertal development among girls, he said. "The heavier you are, the earlier you develop. The earlier you develop, the earlier you hit menarche," he said, noting that the 2001 comparison study found that girls currently have their first periods about six months earlier than was typical in 1971.

Scientists are now beginning to understand some of the reasons that obesity may hasten pubertal development. One is a chain of reactions centering on leptin, a hormone that is produced by and occurs in fat cells. Identified in 1994, leptin stimulates the secretion of gonadotrophic releasing hormone, which triggers the pituitary gland to make two other hormones, called luteinizing hormone and follicle-stimulating hormone. These two hormones rouse the gonads, which make the sex hormones and control puberty, he explained.

He said, "The first puberty occurs at the third trimester of pregnancy and lasts for the first three to six months of life, but the brain then shuts it down. Puberty gets turned on again around the ages of 5, 6, 7 or 8, and leptin is a necessary co-factor. It appears to serve as a necessary metabolic agent for puberty to progress at that time."

In addition, leptin may also play a part in the heightened risk for breast cancer through another rather complex chain reaction, he said. Leptin activates the adrenal gland, which makes a number of hormones that can serve as a substrate for estrogens, through the action on an enzyme known as aromatase. Research now indicates that aromatase activity in fat cells is linked to breast cancer risk, he said.

With research studies beginning to show a connection between obesity and earlier development, and between early puberty and heightened breast cancer risk, Biro suggested that humans' stone-age genes are making their presence known in these eat-more, exercise-less space-age times.

Summary of Dr. Biro's presentation at the November 2005 BCERC Scientific Symposium:
Influence of Obesity on Timing of Puberty.
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Know your audience

Effective communication efforts take into account cultural differences

At the 2005 conference on Emerging Topics in Breast Cancer and the Environment Research, three speakers discussed how cultural difference can affect girls' perceptions of puberty and provide clues about the best ways to communicate with them.

Family and other social relationships

Lisa Mills, Ph.D., Division of Behavioral Medicine and Clinical Psychology at Cincinnati Children's Hospital Medical Center, began by describing culture as neither the biological features of race nor the nationality or ethnicity of individuals, but as the customs, norms, values and styles of living that a group of people share.

Within a culture, she said, the family influence is key, and this is especially true as a girl transitions through puberty. She referred to a research study of girls' experiences with menarche (their first period). "In this study, the girls who knew what to do described themselves as being capable when it came to practical aspects of menarche, and they were comfortable handling the transitions that involved having menstruating bodies. Most of the girls who had these types of perceptions were from higher-income families and represented the range of ethnic diversity that was in the sample, which was Caucasian and African American," she said. The same study identified another population of girls who were unprepared and tried to cope with what they viewed as unpredictable bodily changes. These girls were almost exclusively from lower-income families.

"So you can see that there are cultural differences from girls of different economic backgrounds in terms of preparing girls for pubertal changes," Mills said. The study suggested girls who felt poorly prepared for menarche perceived their pubertal processes and their development much more negatively than the well-prepared girls, she added.

In addition, the study showed that families emphasizing an association between menarche and the ability to have babies prompted reactions from the girls that ranged from fear to anger to acceptance.

Based on other research results, Dr. Mills said, urban girls — particularly those who are African-American — feel their bodily development affords them a new social status of maturity. In the study, even much younger girls who had developed breasts or had already started their periods felt they could associate with older girls, she said. "The girls also felt they were expected to give up childhood friendships with boys, including physical contact with male relatives, and dress modestly to deemphasize their physical development."

In summary, she said, communication directed at pre-teen and teenage girls should "consider how social relationships and interactions with significant people, like family and friends, influence their perceptions of puberty."

Latinas and puberty

Pamela J. Maraldo, Ph.D., executive director of Girls Inc. of New York City, focused on puberty in Latinas, who with Asians and American Indians, have a lower rate of breast cancer than either white or African-American women. "When we look at cultural and environmental risk factors for Latinas, the first thing in the literature that strikes you is that Latina culture places a very strong emphasis on family and child-bearing, and since early pregnancy is a protector of breast cancer risk, this may play a role in the lower rate of breast cancer in Latinas," she said.

Conversely, Latina girls in America experience considerable stressors that typically are associated with higher breast cancer risk. For example, she said, when compared to girls of

other cultural groups, Latina girls have a higher rate of depression and suicide attempts. They also must weigh traditional family beliefs that place women in a submissive role against Western culture's ideals of societal equality between the sexes.

"So the question remains: If puberty is such an impressionable stage of life in terms of development of breast cancer later on, why don't these emotional factors in puberty result in a higher rate of breast cancer later on, as is hypothesized often to be the case?" Maraldo asked. The answer lies in several areas, she said:

- Strong family ties may have a buffering effect on stress and other environmental factors later in life.
- "Latinas are emotional, and in terms of developing cancer, this is often a good thing," Dr. Maraldo said. "There is evidence that resilience to stress is associated with how people handle their emotions. This includes the ability to express emotions, even negative emotions. Though Latinas experience high levels of depression during puberty, they usually learn to express their anger very effectively by watching others, including their mothers."
- The church is another factor. "Prayer and the ability to listen to the church's edict of forgiveness has been shown recently in some studies to have a salubrious effect that may well help mitigate the effects of more difficult emotional factors," she said.

The Asian perspective

Asians are a widely disparate group from a vast geographical area and varying cultures. They do, however, share some similarities, said Kathleen Burklow, Ph.D., Cincinnati Children's Hospital Medical Center, Division of Behavioral Medicine and Clinical Psychology.

"Although Asian groups represent a large number of religions, many of the religions share philosophical principles of Confucianism. Those principles highlight social order, hierarchy, loyalty, and respect for and deference to older family members," she s

you're trying to get information out. You can't always do it in a professional arena; you really need to infiltrate family and friends."

Whether a communicator is trying to reach an Asian population or any other cultural group, he or she must consider the target audience's values, beliefs and norms, Dr. Burklow concluded. "This is true whether you are talking about pubertal development; breast cancer prevention, treatment and intervention; or health care promotion. Understanding culture is critical to translating bench-lab results to the community."

Summary of Drs. Burklow, Maraldo, and Mills' presentation at the November 2005 BCERC Scientific Symposium: Cultural Differences in Perception of Puberty.

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Biomonitoring is useful tool

Technique sorts through complexities of exposure to environmental chemicals

Environmental chemicals can be present in water, food and other materials common in industrialized society. They may also be in the air or the soil. Pairing a particular chemical with an effect on human health is fraught with complications, but a technique called biomonitoring can help cut to the chase, according to two speakers at the 2005 conference on Emerging Topics in Breast Cancer and the Environment Research.

"Predicting health outcomes from exposure is a tricky consideration," said Antonia Calafat, Ph.D., of the Centers for Disease Control and Prevention (CDC). "For instance, we don't know why some people respond differently to similar exposures." Genetics, demographic factors, age, sex, geographical location, timing of exposure, diet, and other environmental and behavioral stressors can all affect a certain chemical's impact, she said. Biomonitoring promises to begin cutting through the complexities, and Dr. Calafat is now involved in the early stages of a major study of environmental-chemical exposure in U.S. girls.

What is biomonitoring?

Biomonitoring is an especially useful tool for exposure investigations, because it assesses the dose of a chemical in a person's body through such means as a blood or urine sample, said Janice Barlow, R.N., of the Marin Breast Cancer Watch in San Rafael, Calif. Her organization helped lead a Bay area community forum to discuss community biomonitoring projects.

The technique allows researchers to detect exposure to environmental chemicals that enter the body via ingestion, inhalation or dermal contact, and whether they are long-lasting or flushed through the body quickly. Those that remain in the body for days, months or even years are called persistent chemicals, she said. "Examples are the persistent organic pollutants, such as dioxin, PCB and DDT, that are stored in adipose (fat) tissue. These are of most concern to lactating women because a portion of the internal dose of those chemicals can end up in breast milk, and can be passed on to the infant during breast feeding."

Many researchers and others have become increasingly concerned about the second main group of environmental chemicals, which are called non-persistent chemicals. Some of these have been tied to a heightened breast cancer risk. These chemicals move quickly through the body and to the kidney, where they are passed in the urine, she said. Non-persistent chemicals are found in such sources as pesticides and phthalates.

By detecting exposure in the body, Barlow said, biomonitoring can capture "unique individual exposures through food, such as mercury in fish; from products, such as those containing phthalates; and from workplace and home exposures, such as lead." It can also yield detailed comparisons of exposures between populations in different areas or of different ages or ethnic groups. Sometimes, data from these studies can lead to changes at the local, state and national levels, she noted. "An example is a study showing that women living in the Bay area (of California) had very high levels of flame retardants, and as a result of that, the California legislature passed a ban on flame retardants that will go into effect in 2008."

In addition, she said, biomonitoring data can help validate models of exposure or evaluate intervention strategies, such as the impact of phasing out lead from gasoline, paints and industrial processes.

The study

The large-scale, multi-site study of environmental-chemical exposure in girls will include biomonitoring of blood and urine samples from girls who are 6 years old and older, said Dr. Calafat. "Before undertaking this large study, we thought it was important to check the coordination and the logistics of collecting samples at different sites, sending them to CDC, and then, once at the CDC, to distribute the samples to the different labs that will do the analyses," she said. For this purpose, a pilot study was devised at CDC in collaboration with the Breast Cancer and the Environment Research Centers in New York City, Cincinnati and San Francisco.

Earlier this year, each center received exacting instructions on the methods for taking the biological samples, and for labeling, handling and shipping the samples to the CDC. All three centers are taking urine samples, and two are also taking blood samples. She commented, "For some chemicals ubiquitous in the environment, care must be taken to avoid potential contamination of the sample during collection and handling." Once at the CDC, the samples go to CDC laboratory personnel who use biomonitoring techniques to screen the samples for various environmental chemicals, such as phenols, phthalates, phytoestrogens, and persistent pollutants.

Although Dr. Calafat had begun receiving the first samples three weeks before the conference, she already had some preliminary results on exposures to bisphenol A and phthalates, both of which are found in plasticizers commonly used in packaging and other products, and have been implicated in a possible rise in breast-cancer risk. The initial findings show a considerable variation in concentrations between the centers and also among the samples at each center for both bisphenol A and phthalate metabolites. Metabolites are compounds that form when a chemical breaks down.

She will continue to keep a watchful eye on the pilot study procedures, and with good results, will then proceed to the large-scale biomonitoring project.

An emerging science

Despite the wide-ranging benefits that the biomonitoring technique already demonstrates, it is still an emerging science, Barlow acknowledged. For example, reliable biomonitoring tests are not available for all chemicals; researchers frequently find it difficult to obtain data on non-persistent chemicals because of their short time in the body following exposure; and large-scale sampling can be both expensive and time-consuming. Even after data are finally collected, she said, their interpretation can be difficult.

Social and ethical questions can also arise, she said. The Bay area community forum, which comprised researchers, members from breast cancer and environmental advocacy groups, health officials and community members, addressed some of these issues. They ranged from the level of community involvement in deciding what chemicals are biomonitoring to the type of information that should be released to the public.

Better indicators should be used to determine cancer risk, researcher says

The number on the bathroom scale or even a person's body mass index are not enough to determine a person's risk of breast cancer, said one of the speakers at the 2005 conference on Emerging Topics in Breast Cancer and the Environment Research. Better indicators are the waist-to-hip ratio and the types of fat consumed, said Deborah Clegg, Ph.D., University of Cincinnati. She also proposed that calorie cutback, rather than weight loss, may protect against breast cancer as well as its recurrence.

"Obesity per se is not as critical as where body fat is distributed," said Dr. Clegg during her presentation on "Dietary Restriction, Meal Anticipation, Fatty Acids and Carcinogenesis." Obesity is rampant in the United States today, as indicated by the staggering percentage, 63 percent, of Americans that are considered to be overweight and/or obese. "Obesity" is defined by a body mass index that is greater than or equal to 30. Body mass index (BMI) measures weight in kilograms divided by height in meters squared.

"Obesity is highly correlated with increased incidence of post-menopausal breast cancer, and I believe this is related to your body fat distribution. I'm going to argue that body mass index should not be the measurement of choice; we should use body fat distribution," she stated. "As we age and go through menopause, most of our fat starts to be accrued in the abdominal area, and we believe this may be critical for breast cancer risk."

Body fat distribution typically takes one of two paths, which can be identified by a waist-to-hip ratio, she said. "Women store more of their fat in and around their hips. This is the fat that is mobilized when we breastfeed our children. When we have fat in our hips, we are actually protected from breast cancer risk." Men, on the other hand, usually store their fat in and around their abdominal area. This fat is the most readily utilizable fat, Dr. Clegg said. In the hunter-gatherer days of early humans, men had to draw quickly from this energy store "to run from a bear," she said.

The problem for women arises when their fat shifts into the abdominal area. She explained, "This typically happens during menopause, when we also become more prone to the diseases that are associated with obesity, including breast cancer. Fat in the abdominal area is associated with insulin resistance, which is, in turn, associated with increased recurrence of breast cancer as well as decreased survival. Insulin resistance is also an indicator of post-menopausal breast cancer risk."

She encouraged women to learn their waist-to-hip ratio by dividing the waist measurement by the hip measurement. "Ideally, women should have a waist-to-hip ratio less than 0.8." If women find their ratio is too high, she recommended exercise to steer the body away from the male pattern of body fat distribution and its related insulin resistance.

Dr. Clegg suggested that different dietary fatty acids have an impact on body fat distribution. Three significant groups of fatty acids are n-3 and n-6 fatty acids, also known as omega-3 and omega-6 fatty acids, and monounsaturated fatty acids, like olive oil. Her lab is testing whether a diet high in each of these fatty acids confers breast-cancer protection or promotion.

"The n-3 fatty acids include canola, flax seed, soy beans, leafy green vegetables and fish oils. These are incorporated into the cell membrane and are anti-inflammatory, which is probably beneficial for lowering breast cancer risk," she said. The Mediterranean diet, which has olive oil as a staple, also appears to yield a protective effect against breast cancer. She continued, "The n-6 fatty acids, which are

found in safflower, sunflower and peanut oils, increase the so-called DNA adducts, which are seen in higher frequency in breast cancer patients."

She remarked, "We believe that if you make a nutritional or dietary change, specifically with fatty acids, you can have a dramatic impact on your propensity for breast cancer. We recommend a diet that is relatively low in fat, and includes more monounsaturated fat, as well as sources of fish oils and other omega-3 fatty acids. We also recommend a reduction in the consumption of n-6 fatty acids."

Dietary restriction can be a key factor in the fight against breast cancer, too, she said. "Dietary restriction is arguably the most potent physiological approach to the prevention of breast cancer. What's really important is that you do not actually have to lose weight to have the beneficial effects associated with dietary restriction. The key is providing limited access to nutrients." She added, "Animal models show that dietary restriction decreases the magnitude of the carcinogenic response. It inhibits cell proliferation, it increases apoptosis or natural cellular death, it decreases tissue vascularization (tumors need vascularization, or blood vessels, to survive and grow), and it works with estrogen prone-tissues as well as non-estrogen-prone tissues."

Dietary restriction involves what she called an "eating paradox." She said, "If you think about it, eating is actually a stressor. Your body has to mount a huge hormonal response every time you eat. You have an increase in insulin, you have activation of digestive hormones, you change your metabolic rate — a whole host of things have to happen when you eat a meal." She has just received a grant from the American Cancer Institute to study laboratory rats that are "meal-restricted." The animals receive their food at programmed times throughout the day, which allows their bodies to prepare for meals. A series of hormonal responses are activated prior to a meal, and she believes these responses are beneficial in providing cancer protection.

She added, "We believe our findings will have clinical relevance, because if we determine that eating meals at planned times each day and eating diets that are rich in specific fatty acids is chemoprotective, these findings could be easily incorporated into human schedules."

Summary of Dr. Clegg's presentation at the November 2005 BCERC Scientific Symposium:
Dietary Restriction, Meal Anticipation, Fatty Acids, and Carcinogenesis
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BCERC research sets the stage for answering tough questions

Which foods, chemicals and other environmental factors might affect breast cancer risk? The scientific community currently has few answers, but the Breast Cancer and the Environment Research Centers (BCERC) has set the stage to bridge that gap, said Gwen Collman, Ph.D., of the National Institute of Environmental Health

This is where the BCERC comes in, she said. The centers originated in response to earlier efforts led by the National Cancer Institute and National Institute of Environmental Health Sciences (NIEHS). During the 1990s, she said, the two institutes funded studies that focused primarily on DDT and its metabolites (the chemicals into which DDT breaks down in the body), on PCBs and other industrial chemicals, and on polycyclic aromatic hydrocarbons, which are present in cigarette smoke and air pollution, she said. They also created a geographical information system, or GIS, to map contextual and ecological information about exposures, which ran the gamut from water records to the locations of Superfund sites.

"As those efforts continued, we decided at the NIEHS that we needed some mechanistic science that would look at the timing of a variety of environmental exposures to see if you could find any elevated risk of developing breast cancer in laboratory-based animal or experimental models," Dr. Collman said. The institute solicited grants and funded a number of projects. At the same time, it was actively working with the National Breast Cancer Coalition and other advocacy groups. "We had a very strong appreciation for the role of the advocates for their voice, for their comments, and for their oversight as being an important part of the research."

The melding of views became more pronounced during a 2002 brainstorming meeting. "We used the results of that advocacy-scientist partnership meeting to come up with a number of areas that we thought would fill bottlenecks and gaps in the research, and we started to craft a program (which would become the BCERCs) that would integrate some of those components as much as possible into a working structure. One of the most interesting points of the brainstorming meeting surrounded the real lack of information about puberty and the changes that occur in the mammary gland structure and function at that time." With such information about the process of breast development and sexual maturation, she said, "we could learn about exposures during puberty that would possibly affect later breast cancer risk as an adult."

Based on that meeting, the BCERC program formed. It is a network of four, collaborative research centers, which include scientists, clinicians and advocates, with a charge to "define in depth how a discrete set of environmental factors interacts with a woman's genetic makeup to influence puberty." Each center also has a Community Outreach and Translation Core to interact with advocate and community organizations.

The potential contributions of the BCERC are many, she said. The initiation of new research through this seven-year program will permit studies that follow girls through the critical period of puberty. "For example, we have very limited information in the literature or even in a database that says: "If I dose at a particular chemical at a

certain time – whether it is gestation, early childhood or puberty – this is what happens at the molecular level to the mammary gland." We hope to be able to have information available on a number of exposures, dosed at different times, and their effects on breast tissue in animal models during these windows of vulnerability. That will be an enormous contribution." Journal articles resulting from these and other studies will form the foundation for future scientific projects as well as discussions about environmental stressors and breast-cancer risk.

The studies may also influence government policy, she said. "Congressional staffers are being asked to look at bills to support more work in this area, but they need to see additional evidence that it is worth the taxpayers' dollars to continue to move in this direction."

By the end of the BCERC program's seven-year run, she envisions a much greater opportunity for researchers to conduct targeted studies that will begin to tackle the public's questions. "There's a lot of work to do. There are a lot of chemical exposures, non-chemical exposures like radiation, and dietary factors, and all of those things are part of the center projects. If, after amassing in seven years a body of literature that is peer-reviewed, scientifically accepted and published, we show compelling evidence of a link between environment and breast cancer risk, then the next generation of scientists will have a better basis from which to look at different strategies and questions more directly related to breast-cancer risk."

Summary of Dr. Collman's overview presented at the November 2005 BCERC Scientific Symposium.

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But is it ready for prime time?

Hot, new technology shows promise for determining breast-cancer risk

Although they have received a great deal of attention in the press, mutations in the BRCA1 and 2 genes are responsible for only a small percentage of breast-cancer cases. Since breast cancer is a genetic disease, science needs to look for variations in other genes to explain what causes the disease in the majority of the women and men who get it. A recent advance in genetics may help solve the riddle by looking for tiny differences in a person's overall genetic makeup, or genome, said Jessica Everett, M.S., who is a genetic counselor at Cincinnati Children's Hospital Medical Center.

"The big hot thing that people are talking about are common changes in the genome that are called single nucleotide polymorphisms, or SNPs (pronounced snips)." A person's genetic makeup is derived from his or her DNA, a long chain of chemical compounds, known as nucleotides or base pairs. These nucleotides come in just four varieties, designated by the letters A, T, G and C. Everett explained, "A SNP is just a change in the DNA sequence of one letter. When we say they are 'common,' we mean that if we looked at 100 people, probably 99 of them would not have the change, but one would."

Scientists currently know of at least 10 million different kinds of SNPs that can occur in humans, she said. "That accounts for the reason we look and behave differently from one another." It also affects a person's susceptibility to diseases like breast cancer. She explained, "There is a lot of buzz around the idea that some these little variations may individually have a small impact on a person's breast cancer risk, but when you add those particular SNPs together, that may be enough to have a big influence on the individual's risk for breast cancer."

Although it seems straightforward, the determination of an individual SNP's impact on breast-cancer risk is anything but, Everett said. "The way this kind of study works is that researchers gather a group of women who have breast cancer and a group of women who do not, and then look at a particular SNP location." Perhaps they find that the SNP is present more often in the women who have breast cancer by a ratio of 9 percent to 5 percent. "The idea is there may be some type of connection there. Maybe they're finding that genotype (form of the gene) in women with breast cancer, because it is somehow related to why they got breast cancer." However, she cautioned, "This doesn't necessarily tell us there's a direct cause and effect. It only tells us that it seems there might be something going on here."

The relationship between a certain SNP and cancer risk becomes thornier because different SNPs can act against each other or can cooperate with one another. "We know that individual genes certainly don't act independently of each other, so looking at variation in one SNP is not even going to come close to getting at the complexity of the situation."

She pointed to a study of SNP interactions as an indication of the difficulties in determining the importance of certain SNPs to breast cancer. The researchers in the study considered only 10 of the different SNPs that might be related to breast-cancer risk. When they looked at the number of genotypes that could arise from combinations of two or three SNPs among those 10, they counted more than 16,000 different genotypes, she said. "And that doesn't even get close to understanding how all 10 of them interact together."

The task is daunting, but studies of SNPs are making important inroads, she said. "We're now at the stage where we can genotype a person at probably 90 different SNPs and have the result in a couple of days. We can do this quickly, we can do it easily, and it's relatively inexpensive." This is also presenting a problem, she noted. "Because we can do it quickly, easily and inexpensively, and because we're dealing with consumers who want to know their risk and how they can do something to change it, we're starting to run into situations where companies are coming to market with risk-prediction tests based on SNP associations. What we need to think about as scientists, researchers, health care providers and health care consumers is: Is this really ready for prime time?"

One currently available test is an example. It claims to determine an individual's five-year and lifetime breast-cancer risks by screening for 90 SNPs in 78 genes, she said. "They send you back a piece of paper that says your five-year risk for breast cancer is (for example) 12 percent and your lifetime risk for breast cancer is 30 percent, so good luck," Everett recounted. Unfortunately, she said, clinicians don't really have good, clear recommendations to give women based on these kinds of risk numbers. "The first thing that comes to my mind when I find these kinds of tests for sale on the internet is whether it's OK for us to offer tests to patients outside of a research setting when we don't know if they are clinically relevant. My argument would be that that is irresponsible, but I'm certainly not the only one having a voice on the issue."

Ethical questions aside, the research is continuing at a fast pace. Everett commented, "Cancer is a genetic disease. Cancer happens because things go wrong with genes, and it's this kind of SNP testing that really shows a lot of the promise." She added, "Coming at this from a clinical perspective, my big question is always about what we are going to do differently. How is this going to be clinically relevant, and at that point, are we ready to talk to patients about doing this particular kind of testing?"

Summary of Ms. Everett's presentation at the November 2005 BCERC Scientific Symposium:
Critical Issues in Biomonitoring and Genotyping
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Puberty-tracking system aids researchers, too

Some studies suggest that menstruation at an early age, a prolonged period of puberty, or other developmental anomalies during the pre-teen and teenage female years may foretell an increased risk of breast cancer later in life. This has turned a spotlight on a clearer picture of what exactly *is* normal when it comes to pubertal development in girls.

One of the primary tools that epidemiologists and other clinicians use to follow a girl's progress through puberty is the Tanner staging system, also known as the sexual maturity rating, that breaks down puberty into discrete steps, said Dr. Louise Greenspan, M.D., Kaiser Permanente Medical Center, San Francisco. Dr. Greenspan explained the steps in the staging system and the associated age ranges and averages, and described the system's history during the 2005 conference on Emerging Topics in Breast Cancer and the Environment Research.

Developed in 1969, the system grew out of a two-decade-long study of girls as they transitioned through puberty, she said. "The Tanner staging system is named after Dr. James Tanner, who was a British pediatrician. He performed a longitudinal study in which the subjects were observed repeatedly over a period of time in the same context." In all, the study included 192 girls, all of them white, British and living in a children's home, she said. Some children were orphans and some came from broken homes. Over the study's 20-year period, she described, the girls underwent examinations and photographs every three months. Dr. Tanner and others in his research group reviewed the collected data and compartmentalized what is a continuous process of development into five stages.

The Tanner staging system evaluates both breast development and pubic hair, and Dr. Greenspan focused her talk on the breast-development portion.

Stage one

This stage is the period before pubertal development begins, she said. The breast shows no outwardly noticeable changes.

Stage two

Also known as thelarche, a breast at Tanner stage two has an enlarged areola, a the papillary (nipple) mound that may be visible, and a breast bud that is palpable (noticeable to the touch) lying under the areola, she described. "In the Tanner study, the average age of thelarche was 11.15 years, with a range of 8.5 to 13 years." Other contemporary studies done in the United Kingdom, United States and Hong Kong at or around the time of the Tanner study showed a range of 9.9 - 10.8 years. A 1992-93 study, known as the Pediatric Research in Office Settings (PROS) study, of 17,000 U.S. girls had results a bit younger than the Tanner study, she said. Dr. Greenspan said, "The Caucasian girls averaged 9.96 with a range of about 7-12; and the African American girls were even younger."

Stage three

In Tanner stage 3 breast development, the bud enlarges beyond the areola, the areola experienced early changes including pigmentation, and small glands, called Montgomery glands, form on the areola. "There is further breast enlargement, but there is no separation of the contours of the areola from the breast. This is all one mound," she explained. The age attainment of stage three in Tanner's study was 12.15

years. She added, "The contemporary U.K. and U.S. studies reported 11.2-11.4 years, which is consistent with the PROS study, but is significantly later than the African-American girls, who attained breast stage 3 at a mean of 10.19 years."

Stage four

The areola and nipple project above the contour of the breast to form a secondary mound in stage four, Dr. Greenspan said. The areola becomes more pigmented and enlarged, and nipple also becomes pigmented. "This is the most variable of all the stages," she commented. "In fact, in the Tanner study, some girls skipped stage 4, and went directly from Tanner Stage 3 to Tanner stage 5." In the Tanner study, the mean age of Tanner Stage 4 was 13.1 years.

Stage five

"Tanner Stage 5 breast development is the mature, adult breast," she said. "There is projection of only the papilla with recession of the secondary mound back to the contour of the breast, and there is a further increase in breast size." Interestingly, of the 57 girls who reached stage 5 in the Tanner study, four of them regressed to stage 4, she said. "People think that breast development is a linear process, but longitudinal studies have shown that there is some hormonal fluctuation and girls can go back." In the Tanner study, the mean attainment of stage 5 was 15.3 years with a range of 11.8-18.9 years. In other contemporary studies, the average age was about 13.8.

Other information from the Tanner study

Menarche, or the first menstrual period, is not part of the Tanner staging system. "You need a certain amount of estrogen to menstruate, but it can happen at Tanner stage 2, 3, 4 or even 5. It's very interesting that the response of the vaginal mucosa and the vaginal lining to estrogen and progesterone is different from what's happening in the breast," she said. In the Tanner study, 25 percent of the girls had menarche by stage 3, and 60 percent by stage 4. The average age was 13.5 years. In comparison, the contemporary U.K. and U.S. studies showed 12.8 and 12.9 years, while the PROS study revealed average ages of 12.8 for Caucasian girls and 12.1 for African-American girls.

The Tanner study also provided a view of puberty's span. In it, girls made the transition from thelarche to menarche, or the onset of breast development to the first menstrual cycle, in an average of 2.3 years. The range was 0.5-5.75 years. She commented, "I suspect that the girls at both ends were abnormal, because 0.5 is a little quick and 5.75 is delayed puberty. In fact, if there is more than three years between thelarche and menarche, it is considered delayed puberty." The study also showed that the time from stage 2 to the complete breast maturation of stage 5 averaged about 4.2 years.

Dr. Greenspan noted that this data is helping researchers today to gain a clearer picture of what constitutes normal development, and will assist in current and future studies of developmental trends.

Summary of Dr. Greenspan's presentation at the November 2005 BCERC Scientific Symposium: Measurement of Normal Human Breast Development During Puberty.

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Puberty is a key period

Progesterone's role in breast-cancer risk

"We think that puberty may be a time of sensitivity to things that can impact on breast development, and the impact on breast development may have a bearing on future breast cancer risk," said Sandra Haslam, Ph.D., of the Michigan State University Breast Cancer and the Environment Research Center. "The underlying basis of the BCERC is to try to understand how pubertal development is regulated and then, once we have a basic understanding of the underlying mechanisms of development, investigate how environmental stressors affect breast development and may impact breast cancer risk"

With that in mind, she has focused her research on the role of progesterone, which is one of the two major female hormones, in breast development during puberty. The other primary female hormone is estrogen. She said, " Researchers have focused for years and years on estrogen, and people continue talking about estrogen, but if you look at the risk factors for breast cancer, many of them are also associated with exposure to progesterone. These include early onset of menses, late menopause and an early pregnancy." The data on menopausal combined hormone replacement therapy reveal that estrogen plus progestin, rather than estrogen alone, is linked to highest breast-cancer incidence. Dr. Haslam added, "When scientists look at the impact of the estrous cycle on breast tissue in animals and in humans, they consistently find that the greatest amount of proliferation is found during that phase of the cycle when progesterone is present."

She is particularly interested in progesterone's impact at puberty, because the hormone directly stimulates intense growth and expansion of breast epithelial tissue, she explained. Only when scientists understand more about the normal process of breast development and how it is regulated, she asserted, can they begin to understand the effect of diet and other environmental stressors on that development.

Dr. Haslam's lab is contributing the knowledge base for normal breast development by examining two types, or isoforms, of progesterone receptor in mouse and rat mammary glands. These two receptor isoforms, known as progesterone receptors A and B (PRA and PRB), provide the sites for progesterone to dock on the breast cells. Like other hormone-receptor relationships in the body, it is only when progesterone is docked that it becomes active in the cells. The PRA isoform is also remarkable because, according to studies, the receptor may have some function even in the absence of progesterone, she said. " It's very intriguing, because 60 percent of the cells in the pubertal mouse mammary gland have only that isoform of the receptor. The notion that it may be operating by itself tells us that we don't know nearly enough about it or about progesterone."

To study the two isoforms, she and her lab are investigating PRA and PRB in mouse and rat mammary glands. Interestingly, the genes in mice express (produce) only PRA during puberty, while the genes in rats (and in humans as far as we know) nearly always express both PRA and PRB. This PRA-only period in the mice presents a unique opportunity to identify the specific function of that isoform, Dr. Haslam said. "This is important, because PRA is very highly expressed during puberty in mice and rats and we really don't yet know what it's doing. We would never be able to figure it out either in the human or in the rat, because both PRA and PRB are present at almost all times."

Although her research is still under way, her lab has already learned a great deal about breast development, as well as the two receptors' activities, in the mouse model. "In the mouse mammary gland, the major development during puberty is the formation of ducts and that occurs through specialized structures called end buds," she said. The ducts are internal structures that will eventually convey milk to the breast's nipple. By 17-20 weeks, when the mouse mammary gland is fully matured, the mammary gland still has a predominantly ductal organization. With each estrous cycle, some sidebranching of the ducts and development of alveoli occurs, she explained. The alveoli are small round clusters that participate in delivering milk to the ducts. "During pregnancy, we see extensive development of alveoli and the formation of lobules, which become the lactating structures. Finally, after lactation and involution (the post-weaning phase), we have a regression, but it doesn't go back to a pre-pregnancy state," she said.

The receptors also change during breast development. Dr. Haslam's lab found that the mouse expresses PRB only during pregnancy and after involution, but mainly expresses the PRA isoform in the non-pregnant state. She added, "PRA is most highly expressed during puberty in the mouse, whereas PRB is present during lobule formation and appears to mediate that formation." She added, "In mice, only the fully mature gland responds to the exogenous progesterone by producing extensive sidebranches and lobules. This is accompanied by the induction of PRB and a downregulation of PRA."

The rat, which more closely mimics the morphological features of human breast development, has a maturation process and pattern of PR isoform expression that is somewhat different from the mouse, she said, and she is planning to present those results in an upcoming paper.

Ultimately, Dr. Haslam would like to study human tissue to gain a clearer picture of breast development. Through these studies, she hopes to lay the groundwork for future investigations of progesterone's role in breast-cancer risk, especially at puberty when environmental stressors may have a significant impact.

Summary of Dr. Sandra Haslam's presentation at the November 2005 BCERC Scientific Symposium: Normal Mammary Gland Development Characterizing Pubertal - Adult Transition in Mammary Gland Development in the Mouse and Rat Models.

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Two studies show U.S. girls are developing earlier: Now what?

Two prominent studies in the 1990s surprised medical professionals and researchers alike when they reported that U.S. girls were entering puberty and attaining their first menstrual periods at younger ages than earlier analyses had shown, said Marcia E. Herman-Giddens, lead author of one of the two 1990s studies. She reviewed the current understanding of puberty and future research areas in her keynote speech, "Sexual Maturation in U.S. Girls: What Do We Know and What Should We Be Asking?," at the 2005 conference on Emerging Topics in Breast Cancer and the Environment Research.

Herman-Giddens, P.A., Dr.P.H., University of North Carolina School of Public Health, explained that her study, called Secondary Sexual Characteristics and Menses in Young Girls, conducted by PROS or Pediatric Research in Office Settings of the American Academy of Pediatrics, sampled more than 17,000 Caucasian and African-American girls seen in pediatric practices across both the United States and Puerto Rico. Both PROS and the second major study in the 1990s, called NHANES or National Health and Nutrition Examination Surveys, documented the ages of girls at various stages during puberty.

Their results countered the conventional wisdom, which was mostly based on a classic 1969 study of British girls and on a 1963-70 U.S. study. "That's one of the reasons it was quite upsetting when PROS and NHANES data came out," Dr. Herman-Giddens said. For example, she noted, the 1963-70 U.S. report showed the average age of the first menstrual period was 12.8 in white girls, and 12.5 in black girls. "In NHANES collective data from 1988-1994, there was a statistically significant drop over the 25-year period for white girls down to 12.6, and for black girls to 12.1."

The lowering of ages in attaining pubertal development should demand the attention of the scientific community and the public, she said. "Two of the issues that I think are important and should be quite concerning are: How far down is this going to go? and Is it healthy?" She added, "We need more data about the timing of pubertal development, as a conference like this points out. We need ongoing cross-sectional data in order to track trends among different cultural groups, and we need more longitudinal studies."

An understanding of pubertal development is an extremely important public health issue for many reasons including that the timing of development might be tied to increased breast cancer risk, she said. In addition to time of onset of pubertal stages, studies of the pace of puberty are also important. According to PROS and NHANES, she said, "For white girls, 2.5 years is the average for transition from the onset of breast development to menses. It's a little bit longer for African-Americans. What this shows as far as implications for breast-cancer risk, we don't know, but this is a question to consider."

Besides timing and pace of puberty, she said many other research areas demand attention. Some of these include:

- the impact of sexualizing children in the media — She displayed advertisements from widely available magazines showing pre-teens and teens in suggestive poses. "Some studies indicate exposure to erotica raises sex hormones in adults," she said. She asked whether teen ads are increasing levels of female hormones in young girls, too, and are possibly connected to their earlier pubertal development.

- stress and changes in family structure – Homes with absent fathers can be especially stressful and may affect the pace of puberty, she said.
- obesity – "Our kids don't go outside and play, they have too much too eat, too many calories, too much protein – exactly what is done with livestock to get them to mature and grow more quickly. For instance, schools have stopped P.E. classes, they have stopped recess, and yet they have junk food in the schools, such as soda machines." As young boys and girls have become increasingly overweight during the past 20 years, she said, "breast cancer has increased by about 25 percent in males and about 15 percent in females."
- additive hormones – Numerous foods and drinks contain growth and bioactive sex hormones, and non-food items contain hormones that may have the potential to affect development, she said.
- antibiotic use – "Some children receive a great deal of antibiotics for such things as ear infections. Since antibiotic use is linked to growth enhancement in animals, what is it doing in children?"

In summary, Dr. Herman-Giddens said, a wide variety of research studies should be undertaken to not only understand what constitutes normal pubertal development among different cultural groups, but also to gain an appreciation for the potential impact of diet, obesity, environmental chemicals, the influence of the media, cultural changes, and other individual stressors, as well as their cumulative effects, on breast cancer risk.

Summary of Dr. Herman-Giddens's keynote presentation at the November 2005 BCERC Scientific Symposium: Sexual Maturation in US Girls: What Do We Know and What Should We Be Asking?
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Common, estrogen-mimicking chemicals found in plastics affect genomic composition of rat mammary gland tissue

Compounds such as bisphenol A (BPA) and butyl benzyl phthalate (BBP) that have xenoestrogenic effect are found in the plastic packaging used for most foods, in dental sealants, in products like compact disks, and in many cosmetics.

As part of studies funded by the NIEHS, Jose Russo, M.D., F.A.C.P., of the Fox Chase Cancer Center and Coral Lamartiniere, Ph.D, of the University of Alabama at Birmingham, investigated these two compounds to determine their influence on mammary gland development in an experimental system. Dr. Russo presented the results of research into the two compounds at the 2005 conference on Emerging Topics in Breast Cancer and the Environment Research.

Russo and Lamartiniere tested the effects of BPA and BBP on mammary gland development in laboratory rats by exposing pre-pubertal animals through their mothers' milk. The results were striking.

By the time the rats had attained puberty at the age of 21 days, the genetic signatures — the patterns of active and inactive genes — in their mammary glands had changed, Dr. Russo said. The genetic signature is a snapshot of those genes that are upregulated, or turned on, and those that are downregulated, or switched off and inactive. Researchers seek genetic signatures for a variety of disease entities, including cancer, to better understand the mechanisms of disease progression and genetic susceptibility. "Among the BPA-treated rats, the mammary glands at 21 days showed upregulated genes related to proliferation and differentiation, whereas at 50 days, the upregulated genes were involved in metabolism, signal transduction and immune surveillance," he said. In other words, from the ages of 21-100 days, the activity of these genes changed, especially in areas that may promote or regulate growth and differentiation.

The 21-day picture of BBP-treated rats also showed an upregulation of genes involved in proliferation, differentiation and cell adhesion (the ability of cells to stick together), but also in tumor suppression, he said.

Besides these differences in upregulated genes, the research group also identified one gene that was downregulated in both the BPA- and BBP-treated rats, regardless of their age. It was a gene called GAD1 that ultimately produces an enzyme known as glutamate decarboxylase 1. This enzyme is important for another compound, known as a neurotransmitter, which helps nerves communicate with one another. Research has shown that the GAD1 gene is often overexpressed, or much more active, in primary breast cancer, and that it could play a part in tumor development.

The research clearly shows that BPA and BBP are having an impact on the genomic composition of the mammary gland, Dr. Russo said. He added that the critical question surrounds the significance of these changes in relation to the susceptibility or refractoriness of this organ to carcinogenesis. Studies are in progress in Dr. Lamartiniere's laboratory to test this issue.

Dr. Russo is a senior member of the Fox Chase Cancer Center, where he serves as director of the Breast Cancer Research Laboratory, and the Breast Cancer and the Environment Research Center. Details of his research appear in "The Proceeding of the American Association for Cancer Research 2005."

Path involving chromosome "caps" may set malignancy in motion

Research has repeatedly shown that a high rate of spontaneous mutations occurs in the genetic makeup of cancerous tumors, but the jury is still out on the cause of this genetic instability and the contributions, if any, of these aberrations to the malignancy. New studies by Paul Yaswen, Ph.D., of the Lawrence Berkeley National Laboratory, suggest that a combination of factors, including the shortening of the caps that sit on the ends of chromosomes, may instigate the process that leads to cancer.

Dr. Yaswen is using surgically-discarded, human mammary epithelial cells grown in culture (in artificial conditions in the lab). He is especially interested in the growth controls that are typical of normal cells, but are absent in malignant cells. Normal cells grow for a while in culture, but then stop in a phase called senescence, which appears to be mediated by a tumor suppressor called p16, he said.

"Interestingly, a minority of cells in culture manage to downregulate (shut down) the suppressor and continue to grow. These cells encounter another senescence arrest called agonescence, and this appears to be due to critical shortening of structures, called telomeres, at the ends of the chromosomes."

Under normal conditions, the telomere end caps protect the chromosomes and ensure that the genetic information (DNA) they contain is passed on properly. Without the caps, the genetic information would be susceptible to damage. This might include the loss of some DNA, the fusing of chromosomes together, or myriad other mutations. Every time cells divide, their telomeres become a little shorter. When they become too short and the genetic information contained in the chromosomes is in jeopardy, the cells stop growing or die.

Unlike normal cells, those in breast tumor tissue bypass these controls and continue growing and dividing indefinitely, Dr. Yaswen said. Results in his lab and others show that a main culprit is an enzyme called telomerase. This enzyme maintains the telomeres. In humans, telomerase is active in fetal tissue, and in adult sperm and eggs, but not in other normal, body cells. Tumor cells, however, are able to activate telomerase, boost the length of their telomeres, and become immortal, he explained. "In normal cells, we think that telomerase is stringently repressed as a mechanism for suppressing carcinogenesis, and it is stringently repressed by more than one independent mechanism."

How, then, do the tumor cells switch on telomerase production? To find out, Dr. Yaswen collaborated with Dr. Martha Stampfer, also at the Berkeley Lab, to examine cell cultures previously treated with benzopyrene, a known carcinogen found in such sources as cigarette smoke. He said, "We did not detect the activity of the telomerase immediately after the carcinogen exposure, but only many generations following the exposure. We now think that the benzopyrene can cause errors in a pathway that's responsible for repressing telomerase, but that other errors have to accumulate before the telomerase can actually turn back on."

He believes that these other errors might come during the period when the telomeres are critically short. This is an especially vulnerable time for the chromosomes, because the telomeres are no longer able to protect the genes contained in the chromosomes and they are more likely to mutate. Normally, this is not a problem, because the cells with critically short telomeres soon stop growing or die. If mutated cells manage to turn on telomerase, however, they can extend their telomeres and become immortal, a critical step in becoming tumor cells.

Dr. Yaswen's lab took this information and tested a gene, called ZNF217, that has been linked to malignancy. "When we put this ZNF217 gene into cells, the telomerase didn't come on again immediately, so we concluded that the ZNF217 gene is not turning on telomerase activity itself." In this case, he believes that the aberrant overexpression of the gene is reducing the tight control of telomerase, and increasing the survival of cells with shortened and therefore dysfunctional telomeres until a second event occurs that finally turns on the telomerase and subsequently lengthens the telomeres, giving the cells a new lease on life.

In summary, he said, "We think that most spontaneous, human, solid tumors arise from telomerase-negative cells, which acquire their malignant changes during this early period of genomic instability that is associated with telomeric dysfunction. Having acquired these malignant changes, the tumor cells reactivate telomerase in order to survive, and in so doing they may acquire additional features which are common in stem cells." Stem cells, seen in fetal development, are cells that are generalized, or undifferentiated, and have the ability to grow into various types of tissue cells, such as lung, heart or muscle cells. These cells require telomerase, which protects their chromosomes and gives them an extended growth period.

Further investigation into the reason that telomerase repression fails could be important in the fight against breast cancer. He said, "We think augmentation of the processes that monitor and prevent the growth of these cells with the dysfunctional telomeres may be useful for the prevention of immortalization and the prevention of malignancy."

Summary of Dr. Yaswen's presentation at the November 2005 BCERC Scientific Symposium:
Modeling Pre-malignant Changes Using Cultured Human Cells.
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