

# IUSCC PINK

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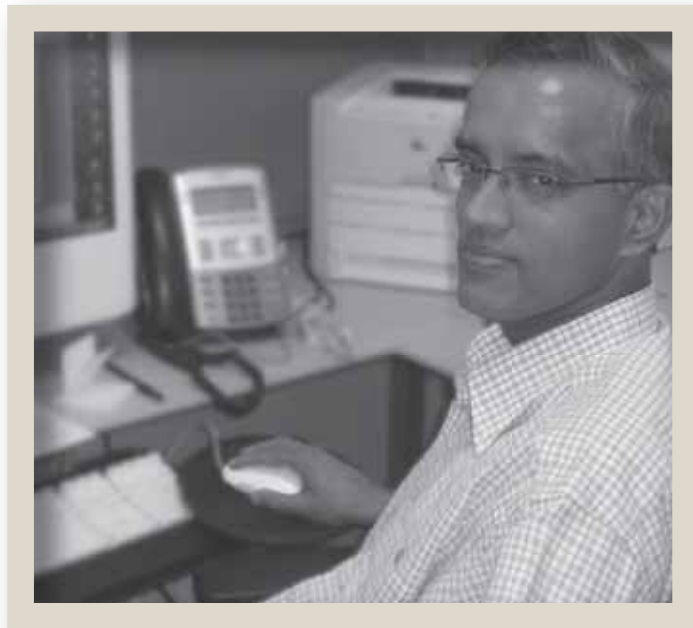
Spring 2010

Dear Friends,

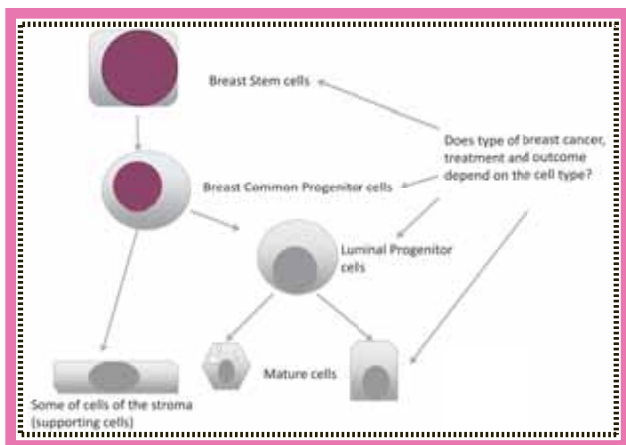
The 19th century pathologist Julius Cohnhein (1839-1884) asked "where does the cancer come from?" He then proposed a theory of "Embryonic Rests" in which excess germ cells from the embryo (during development in the womb) subsequently develop into cancer, linking the origin of life to its end. Scientists have had on-and-off-interest in this stem cell theory of origin and progression of cancer. Renewed interest in this theory started in the late 1990's and currently it is one of the most intensely studied aspects of breast cancer.

To link this theory of breast cancer origin and progression, it is important first to know how normal breast develops and how many different cell types exist in the breast. The normal breast is made up of several types of cells. Epithelial cells, from which most cancers originate, are the major cell type. Other cells, called "stromal cells", play a supporting role

in the development of normal breast, as well as breast cancer. For researchers investigating the origin of breast cancer, epithelial cells are the key cell type of interest. As in other organs as well as our blood system, adult stem cells in the breast differentiate (the act of development from one to many types) to provide different cell types. The figure below shows our current knowledge of how different cell types are generated in the breast.



*Dr. Nakshatri explains stem cell theory.*



Questions in the forefront of current breast cancer research include: 1) Which cell type is more prone for cancer? 2) Does it matter from which cell type the cancer originates? 3) Will knowing the cell type from which the cancer originates helps in diagnosis and treatment?

The latest developments in technology have helped to address these questions. Researchers have used cells isolated from the mammary gland of mouse to first identify cells with stem cell like properties. A single cell implanted into a mouse whose mammary gland has been surgically removed can reconstitute a complete mammary gland. Such a cell is named a stem cell. Stem cells have

unique proteins on their surface compared to other cells. Antibodies that bind to these proteins can be used to "pick" these cells out of the remaining cells. Using antibodies against other proteins, several cell types, which came from these stem cells, have been identified.

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# How many types of breast cancer can stem cell theory of cancer address?

While scientists are pretty sure of different cell types present in the breast and mammary gland, the question is to what extent mouse and human breast cells are similar and whether results from mice explain breast cancer in humans. Also, what is the relationship between these normal cells and different types of breast cancer? Using "gene expression profiling" techniques, researchers have recently reported that several genes present in the mammary stem cells (mouse) are also present in human breast stem cells. Similarly, genes that are present in the mouse mammary progenitor cells are also present in the human breast progenitor cells. These studies have enabled us to

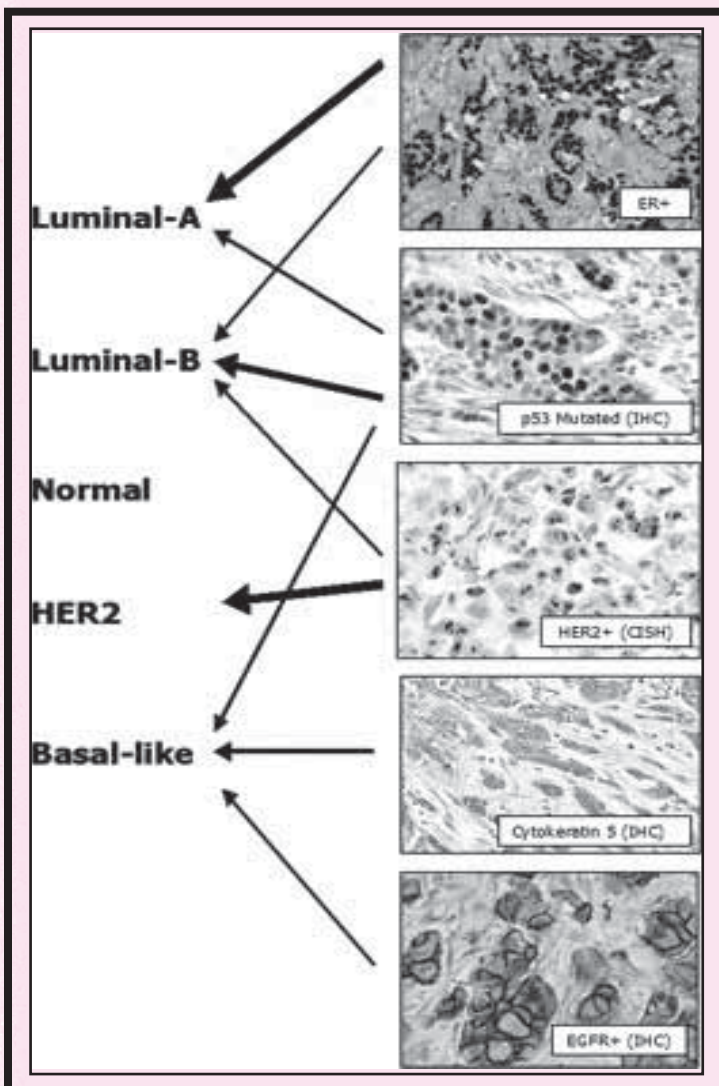
come up with a list of genes that can serve as "markers" to characterize stem, progenitor, and mature cells of the normal breast. Additionally, lists of these markers have provided a hint to the role of these genes in normal breast development. Using these marker sets, one can now ask whether these genes are present in specific types of breast cancers.

## Questions in the forefront of current breast cancer research include:

- 1) Which cell type is more prone for cancer?
- 2) Does it matter from which cell type the cancer originates?
- 3) Will knowing the cell type from which the cancer originates helps in diagnosis and treatment?

Among solid tumors, breast cancer has taken the lead in "molecularly dissecting" cancers into multiple types. In the 1960's, breast cancer was classified simply into two types- Estrogen Receptor-positive and Estrogen Receptor-negative. Estrogen receptor is a protein required for normal breast and breast cancers to grow in response to estrogen. The latest literature suggests that there are as many as 17 types of breast cancer. However, classification into six subtypes is widely accepted and is in clinical practice. Interestingly, expression pattern and levels of genes in majority of these cancer subtypes resemble genes present in normal milk duct cells. Very few breast cancers have similarity to genes present in the breast stem cells. Based on these observations, the current thinking is that Estrogen Receptor-positive breast cancers mostly originate from mature milk duct cells, whereas triple-negative subtypes originate from luminal progenitor cells. We don't yet know where HER2-positive breast cancers originate from. Luminal progenitor cells in patients with BRCA1 mutations are more prone for cancer. Thus, a cancer can have two sets of genes; the first set is similar to genes present in normal cells from which cancer originated and the second set of genes that are mutated in cancer only. This second set of genes distinguishes cancer cell from its normal counterpart.

How does the above knowledge help in finding a cure for breast cancer? Cancers with gene expression patterns more closely related to stem or progenitor



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cells tend to be more aggressive, spread to other organs (metastasize) and respond poorly to chemotherapy. Chemotherapy often kills cancer cells that divide fast. In general, "stem"-like cells-both normal and cancerous- tend to divide slowly and thus escape from chemotherapy and radiation therapy. Researchers have gained substantial knowledge of proteins required for "stem" or "progenitor" cells to survive and differentiate. Some of these proteins have activities that can be used to develop drugs. For example, can we come up with drugs that force stem and progenitor cells to become mature cells so that cancers from these cells are less aggressive? One such example is a protein called c-Kit, which is present mostly in luminal progenitor cells. A new wave of combination therapies can be developed, which will include drugs that would target cell types from which cancer originated and drugs that work on mutations that are found only in cancer cells. This combination therapy will effectively kill all cancer cells rather than killing only fast dividing cancer cells.

We have been using the knowledge gained from these studies to develop biomarkers that help to identify patients who may need extra treatment or patients who may not need additional treatment. For example, patients with Estrogen Receptor-positive breast cancers usually receive tamoxifen or aromatase inhibitors. Not all patients respond to tamoxifen alone. Will it not be useful to find out at the beginning of breast cancer diagnosis whether someone will respond to tamoxifen? We have observed that patients with Estrogen Receptor-positive breast cancers which also contain a protein called FOXA1 do exceptionally well. If one looks at normal breast cells, only mature luminal cells contain both Estrogen Receptor and FOXA1. Our guess at present is that cancers in these patients originated from mature luminal cells and theoretically are less aggressive. The origin of Estrogen Receptor positive breast cancers that do not contain FOXA1 is something of a mystery at present. We are addressing this question using mouse models as well as samples from patients who have received tamoxifen. We have also made progress in identifying markers that help to distinguish basal type breast cancers into different subgroups.

There are several challenges still ahead of us including using the recent knowledge of stem and progenitor cells in identifying new drugs, developing markers to measure the effects of treatment, and simple methods for early detection and classification of breast cancer. However, the current phase of progress gives us the hope that these challenges will be met in the very near future.

## Peach Crumble

2/3 cup light brown sugar  
3/4 cup old-fashioned oatmeal  
1/2 cup natural wheat and  
barley cereal  
1 1/4 cup all-purpose flour  
(divided)  
1 teaspoon cinnamon  
1/3 cup canola oil  
2 (16 oz) packages frozen  
peaches (or 4 cups fresh fruit)  
2/3 cup confectioners' sugar  
1 teaspoon vanilla extract

Preheat oven to 350 degrees. In a bowl, mix together the brown sugar, oatmeal, cereal, 1 cup of flour, and cinnamon. Stir in oil, mixing until crumbly. In another bowl, toss peaches with confectioners' sugar, vanilla, and remaining flour. Transfer fruit into a 2-quart baking dish and cover with oatmeal topping. Bake until bubbly, about 35 to 40 minutes. Makes 8 to 12 servings

This recipe is great for combating constipation. The use of a wheat and barley cereal like Grape Nuts, oatmeal and fruit adds a lot of fiber. Try substituting whole wheat flour for all-purpose white flour for added fiber and nutrition. If you don't like peaches, try other fruits like berries or apples. Cutting back on the sugar in this recipe also makes it healthier. Enjoy this dessert hot with frozen yogurt for a great treat.

# A Door of Hope

## Little Red Door Cancer Agency



Since 1945, Little Red Door Cancer Agency has recognized that cancer takes an extreme toll on cancer patients and their families. Unfortunately, many of those living with cancer lack financial resources, creating barriers to recovery. Therefore, Little Red Door is committed to serving those with cancer in the greater Indianapolis area, including Boone, Hamilton, Hancock, Hendricks, Johnson, Marion, Morgan and Shelby counties, who lack financial means or adequate insurance.

One of the largest independent cancer agencies in central Indiana, Little Red Door Cancer Agency opens doors to reduce the physical, emotional and financial burdens of cancer through a variety of free services, including screening and detection, client services, education and client navigation.

Little Red Door Cancer Agency is able to provide these services through the generous support of the United Way of Central Indiana, the Indianapolis Affiliate of Susan G. Komen for the Cure, grants, general contributions and bequests. About 86 cents of every donated dollar directly benefits cancer patients and the programs Little Red Door provides to the community.

### Screening & Detection

Little Red Door's Screening and Detection Department offers a variety of free cancer screenings because we know early detection is the best medicine for a healthy future. Little Red Door offers screenings for breast, cervical and prostate cancers in the earliest stages to those who qualify based on residency, household size, household income and insurance coverage.

**Mammography Assistance Program**-Assists with clinical breast exams, screening and diagnostic mammograms, ultrasounds and biopsies.

**Prostate Cancer Screenings**-Screenings offered in a variety of Indianapolis locations throughout the year.

**Cervical Cancer Screenings**-Reduced-cost Pap smears are available with contracted clinics.

### Education

Little Red Door's Education Department provides infor-

mation to the community about cancer prevention and early detection. Education programs are delivered to the community through participation in community health fairs.

### Client Services

Little Red Door's Client Services Department provides several free programs to assist cancer patients during their battle against the disease. These services are available to residents of the greater Indianapolis area who qualify based on residency, household size, household income and insurance coverage.

### Transportation

Transportation is available for cancer patients receiving chemotherapy or radiation treatments and for those who have cancer-related follow-up appointments. Vehicles can accommodate wheelchairs and walkers. (Marion County residents only).



### Breast Prostheses and Bras

Available for those with a physician's prescription.

### Incontinence and Ostomy Supplies

Adult diapers, pull-ups, skin protectants and bed pads available on a monthly basis.

## Medical Supplies

**Wound care supplies and lymphedema bandages/garments** provided on an as needed basis.

**Nutritional Supplements (Boost and Ensure)**- Available on a monthly basis with a physician's prescription (Marion County residents only).

**Wigs/Hats/Turbans** -Cancer patients who have lost their hair may visit the Little Red Door Boutique to select wigs and headwear.

**Camp Little Red Door**-Camp Little Red Door, a fun, weeklong camp for Indiana children ages 8 to 18 who are battling cancer or are in remission. Ninety spaces are available each summer at Bradford Woods near Martinsville, IN. Campers may bring a sibling or friend if space is available.

## Client Navigation

Little Red Door's Client Navigation Department works to "fill in the gaps" for breast clients by providing basic information about breast health, the importance of timely follow-up, and community resources to help meet basic needs before, during and after treatment.

Services include, but not limited to, providing contact and program information for local and national resources that help address basic needs, such as transportation, support, rent/utilities, treatment coverage, food, etc.



Services available to residents of the greater Indianapolis area who qualify based on residency, household size and household income.

## Research Study Testing a Treatment for Persistent Cancer-Related Fatigue

Fatigue is the most prevalent, persistent, and disruptive symptom that people with cancer report struggling with. There are many survivors who go months or even years and still struggle with it. Effective treatments for CRF are lacking.

*Study description:* We are testing a seven-week Mindfulness-Based Stress Reduction (MBSR) program. Since MBSR has been shown to be helpful with several of the factors known to perpetuate fatigue (e.g., sleep disturbance, pain, stress, anxiety, and depression), we are doing a controlled study to see if it helps with fatigue. MBSR provides training in mindfulness meditation, gentle yoga stretching, and a variety of coping skills. Study participants will be compensated up to \$125 for participating in this program. The study is funded by the Walther Cancer Foundation and the National Cancer Institute.

*Eligibility:* Adults with any type or stage of cancer are eligible, but you will need to have completed your cancer treatment (surgery, radiation, and/or chemotherapy) at least three months prior to your enrollment in the study. If you are taking ongoing hormonal therapy for breast cancer, you ARE ELIGIBLE to participate.

*When/Where:* The classes will start sometime in the May 31-June 12 timeframe and run for seven consecutive weeks. Class days and times are not yet set, but we may have either a weekend or weekday class, depending on what works best for the majority of those who enroll. Each class will be two hours in length (with Week 6 class being three hours). If you enroll, you will be "randomly assigned" to either receive the MBSR class starting in June or early September. You will be asked to complete a survey 3 to 4 times during the study so we can keep track of your fatigue over time.

*Next steps:* Please call project manager Dr. Shelley Johns to see if you are eligible for the study. You may also call Shelley to discuss the study further or to have her mail a copy of the study brochure to you if you are unable to open the attached version. You may reach Shelley by calling (317) 630-7690 or by emailing her at sheljohn@iupui.edu.

For the History Buffs:

## the Progress of Breast Cancer Treatment

By: Daisy Allen-Pales, DCRP

I never really was a history buff, but lately when people ask me about what's new with breast cancer I can't help but look back. I have been involved in the breast cancer clinical research world for about five years (minuscule compared to most of the IUSCC researchers, doctors and nurses) and it amazes me how things have changed just in that short amount of time. This caused me to think about the timeline of breast cancer and how quickly we are making progress today compared to just 10 or 20 years ago. So, here is a rough timeline some of it is taken from Randomhistory.com. Visit the site for the whole article Phenomenal Woman: A History of Breast Cancer.

"Breast cancer is an ancient disease, and it has been mentioned in almost every period of recorded history. Ancient Egyptians were the first to note the disease more than 3,500 years ago. One nameless ancient Egyptian surgeon describes "bulging tumors" in the breast and states that "there is no cure." In A.D. 200, there are a wide range of pharmaceutical agents to treat breast cancer, such as opium, castor oil, licorice, sulfur, and a variety of salves, as well as incantations to the gods. For the next 2,000 years, breast cancer was a systemic disease, which meant it was a disease of the entire body, not just one localized part. Surgery to remove the tumor or entire breast was not even considered to be an option for a cure since physicians assumed the cancer would just reappear near the surgical site or somewhere else in the body.

In the late 1700's, a French physician took a piece of breast cancer tissue along with a slice of beef and burned them both in an oven and chewed them. Both tasted the same, and he concluded the tumor tissue did not contain unusual amounts of bile or acid, thus disproving the theory cancer was caused by an imbalance of the body's four humors. Physicians then began to search for a new origin of breast cancer, and many argued that its origin was sexual. The hypotheses that the high frequency of breast cancer in nuns was due to lack of sex; without regular sexual activity, reproductive organs, including the breast, started to decay and cancer was the result. Others speculate that women who had regular sex but still developed cancer were practicing "vigorous" sex that could result in lymphatic block-

age. Yet others suspected curdled milk that was caught in the milk glands, depression, childlessness, and a sedentary lifestyle as the cause of breast cancer. During this time, the realization that breast cancer was a localized disease and not systemic lead to the first surgeries to remove the breast and surrounding tissue.

By the mid-nineteenth century, most physicians held that because cancer was a localized disease, surgery was the only hope. William Halstead of New York made radical breast surgery the gold standard for the next 100 years. This radical mastectomy—removed the breast, axillary nodes, and both chest muscles in a single en bloc procedure. Women had to deal with a deformed chest wall, hollow voids under the collar bone and the armpit, chronic pain, and lymphedema. Halstead dismissed these effects as necessary evils; besides, the women's average age was "nearly fifty-five years and they are no longer active members of society" (Olson 1999).

"In 1895, a Scottish surgeon discovered that removing the ovaries from one of his patients shrank her breast tumor. This news spread and soon surgeons were performing "prophylactic" oophorectomies, which involved removing both ovaries and performing a radical mastectomy. Until the 1950's surgeons tried removing different glands throughout the body to reduce estrogen levels, with little luck."

In 1973, one of the first large scale studies on mammography reported a reduction in mortality for women who were screened with the crude mammograms of the time (Strax P 1973). Often times a general x-ray machine mounted on the ceiling was used for breast imaging. In 1975 a World Health Organization survey showed that death rates from breast cancer had not declined since 1900 and it was realized that surgery alone was not the answer (Lee 2000). In 1976, Bernard Fisher published results indicating that simpler breast-conserving surgery followed by radiation or chemotherapy were just as effective as the radical mastectomy, and usually more so.

In the 1980's, the HER2 protein over expression in breast cancer is discovered, which accounts for 25% of breast cancer cases. By 1998 Trastuzumab aka Herceptin, the

first HER2+ treatment is approved for treatment of metastatic breast cancer. During the clinical trial process researchers realized that they needed a test to know which women over expressed HER2. The Herceptest was approved with the Herceptin and is now a standard pathology test performed on breast cancer tumors (Genentech).

During the 1990s, the cause of breast cancer was again being hypothesized; everything ranging from diet, chemical pollution, race, delay in having children, and breastfeeding was up for debate. In 1994 BRCA1 gene was discovered and two years later BRCA2 accounting for 5 to 10% of breast cancer.

In 1998, the first trial of what is now known as Avastin, an antiangiogenic therapy, began at IUSCC. Although the early trials of Avastin alone didn't show the results that everyone had hoped for, they did see promise. After a long tough road in 2008, Avastin was the first immunotherapy drug approved by the FDA for the treatment of metastatic breast cancer in combination with chemo-

therapy. Now as we research this drug in the adjuvant setting, we will have to impatiently wait to know how dramatic an effect Avastin will continue to have on breast cancer treatment.

New drugs such as Tykerb and others, only continue to improve the prognosis of women with breast cancer. Today science is moving at amazing speed. Nanotherapy, genomics, and proteomics will continue to provide better treatments for this disease. As biological discoveries begin to move from the laboratory to the clinic in three to five years, treatments will abound. With mammography machines designed to provide the best imaging possible and recommended screening, discovering cancer is only getting easier. The majority of methods used to detect and treat breast cancer are barely in their thirty's. If the saying is true and 40 is the new 30 then the next 10 years should be very exciting in the world of breast cancer.

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## Breast Cancer & A

*Do bone mets mean you are terminal?*

Typically when breast cancer involves another organ such as the lung, liver, brain, or bone, it is not a disease that can be "cured." The number and success of many of our breast cancer therapies have allowed countless women with metastatic disease to enjoy a good quality of life for many years. Many investigators hope that in the near future we will manage women with metastatic disease very similar to the way we manage a patient with diabetes. Although they might require a therapy for their entire life, it is one that can keep the cancer in remission. Other investigators are devoting their careers to change this paradigm and someday make metastatic disease something that can be cured.

*My sister has a tumor marker of 25 without cancer...I have a tumor maker*

*of 25 with cancer. Should she be concerned?*

Tumor markers are FAR from perfect tests. First the definition of a normal marker is different by different laboratories. Second many women who have cancer do not have an elevated tumor marker. Thus if her number is in the normal range, unless there are other worry some findings, there should be no reason for concern.

*Does triple negative=basal type breast cancer?*

Not necessarily. Basal type BC has been defined by a specific pattern of gene expression, in other words a certain set of genes that influence cancer growth are relatively more active. It is believed that this subtype of cancer is derived from a cell in the breast. It is true however that the majority of cancers with this characteristic gene expression profile are classically HER2, ER and PR negative (Triple Negative), but the overlap is not 100%.

## ARE YOU INTERESTED IN LEARNING MORE ABOUT BREAST CANCER?

Sign up to receive the *IUSCC Pink* Newsletter

Name: \_\_\_\_\_ \*E-mail: \_\_\_\_\_

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\*Newsletters will be sent by e-mail when applicable.

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Or send an e-mail to [calallen@iupui.edu](mailto:calallen@iupui.edu) with the above information.

Do you have a story idea or just something to say about a story you've read in *IUSCC Pink*? Tell us about it! Would you like to share a personal experience? Contact us via e-mail [calallen@iupui.edu](mailto:calallen@iupui.edu), call 317-274-0594 or send mail to the address above.

Past editions of *IUSCC Pink* can be viewed at the IU Simon Cancer Center Web site, [cancer.iu.edu](http://cancer.iu.edu), by selecting breast cancer in the cancer type section (<http://cancer.iu.edu/programs/breast/iuccpink/>).