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Cancers: Breast Cancer

About Breast Cancer

Breast cancer is a leading form of cancer in women and exacts a heavy toll, with over hundreds of thousands of women estimated to die globally every year from this disease. The risk of developing breast cancer can be influenced by many variable factors, some genetic and some lifestyle, with a particularly high incidence in the developed world. Early detection programs are most readily available in the developed world and this has helped improve survival rates in these countries. Men may also develop breast cancer and although it can be equally lethal for them, their risk is about 100-fold lower.

Breast cancers develop as “solid” tumours and are given additional sub-type names according to the cells in the normal breast that they seem to resemble most closely. The normal mammary gland is made up of ducts that connect the milk-producing lobules to the nipple and this entire structure is made up of two layers of cells: an outer layer of “basal” cells and an inner layer of “luminal cells”. Breast cancers vary in the extent to which their cellular composition mimics elements of the normal mammary gland and may be classified on this basis.

Research is a dynamic enterprise that generates a wealth of knowledge. It provides a forum for debating ideas and working them into evidence-based theories. The clinical trial setting puts these theories to the test and may lead to evidence-based medicines that can alleviate symptoms or cure disease. But the process of taking research from bench to bedside is a lengthy one, and demands not only vision but also years of hard work and dedication on the part of scientists, physicians and patients. This document presents basic information about breast cancer and frames the context for the discussion that follows about how lessons learned from stem cell research may help fight this disease. Readers may also wish to peruse additional web resources or speak with their physicians for more information about this disease.

Another characteristic that distinguishes breast cancers is whether the cells in them have become invasive. At an early stage, breast cancers consist of cells that have begun to grow out of control but have not yet acquired an ability to cross the basement membrane barrier that encases the entire normal mammary gland. Because these tumour cells remain in place or ‘in situ’, they are referred to as “in situ carcinomas”. Ductal carcinomas and lobular carcinomas that are non-invasive are called ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS), respectively. Breast cancers identified at this stage are generally curable by surgery and/or local radiation treatment. In contrast, invasive tumours include cells that have crossed the basement membrane into the tissue that surrounds the mammary gland. From there, the malignant cells may invade the lymphatics and blood stream and hence spread to the draining lymph nodes and throughout the rest of the body. When the cells have spread to other sites and established new tumour nodules, these are called metastases. Breast cancer metastases are most often found in the bone, liver, brain, and lungs and their further growth is difficult to eradicate. However, even if a tumour is invasive, it can often be cured if it is confined to the breast. The problem is that it is often difficult to know if this is the case.

Causes, risk factors, symptoms and staging

Breast cancer can run in families, but as far as we know only 5-10 per cent of all cases are caused by an altered gene that is inherited. The abnormal growth, invasive properties and treatment resistance of the other 90-95 per cent of cases are also thought to be caused by abnormalities in genes; but these are acquired not inherited, and hence are unique to the developing tumour population. These abnormalities may affect many aspects of cell behaviour including the control of expression of other genes (epigenetic regulators).

The genetic changes that cause the formation of a particular breast cancer are not to be confused with factors that

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affect the risk of breast cancer development. Risk factors can be subdivided into those that can be altered and those that cannot. Examples of lifestyle factors that appear to affect the risk of breast cancer include smoking, exercise, weight, alcohol use, and exposure to hormones used in contraceptive pills or in in vitro fertilization protocols. Examples of risk factors that are not modifiable include age, gender, family history, starting age of menstruation and menopause, and breast density.

Although many cancers seem to appear abruptly, most actually grow slowly and remain without symptoms for several years. As a result they go undetected until they are fairly well advanced or are picked up by chance. Typical symptoms of breast cancer include: a lump or thickening in or near the breast or in the underarm area; changes in the size or shape of the breast; a dimple (pea d'orange) or puckering in the skin of the breast; an inward turned nipple; fluid discharge from the nipple; and scaly, red or swollen skin on the breast, nipple or areola. A cancer that has acquired aggressive properties, however, can seem to appear out of nowhere and cause death within months. Unfortunately, very little is known about the different biologies that explain these different behaviours and prognoses.

Staging is an important part of breast cancer diagnosis because it can be used to guide therapeutic decisions based on historical experience of particular outcomes after different treatments. In the TNM system of staging, the combination of the tumour size (T), the number of lymph nodes involved (N) and whether metastases are detectable (M) provides details which place the overall stage of the cancer at 0, I, II, III or IV. Some breast cancers have particular cell surface receptors, such as Her-2-neu, that help the cells to grow. Knowing the receptor status of a breast cancer can provide an even more in-depth assessment of the cancer's stage. In addition to staging factors, the likely outcome (or prognosis), may also be affected by the age, health status, and menopausal status of an individual.

Treatments

Conventional treatments for breast cancer include surgery (lumpectomy or mastectomy) that removes the tumour and part or all of the affected breast, radiotherapy (usually localized to the affected breast also), and chemotherapy with or without hormone therapy to kill or shrink the tumour and kill distant metastases. Neoadjuvant therapy refers to any combination of treatments that are given before surgery, and adjuvant therapies are those that are administered after surgery, often in an effort to reduce the risk of recurrence. While chemotherapy and radiation are effective, they can also cause a great deal of collateral damage because they kill cells that divide, whether they are tumour cells or normal cells.

Newer, therapies now being developed are directed at known molecular "targets" in tumour cells in the hopes of improving outcomes and reducing the negative side effects caused by conventional treatments. For example, certain monoclonal antibodies (e.g., trastuzumab) target a specific molecule uniquely expressed on the surface of the tumour cells and thus tag them for destruction by the immune system. Although the use of trastuzumab has greatly improved the treatment of Her-2 positive breast cancers, cells that are resistant to the drug are usually already present and eventually grow out causing the cancer to come back (recur). What is needed are several non-cross-reactive agents that could be given simultaneously to prevent this, which is the goal of much current research (e.g., with tyrosine kinase inhibitors like lapatinib and PARP inhibitors that block DNA repair mechanisms).

How Can Knowledge of Stem Cells Help Breast Cancer?

The cancer stem cell hypothesis

The concept that cancers are propagated by a small subset of cells with stem cell properties has existed for more than a century. This concept is extremely important because it implies that these cells must be eliminated to achieve cures but may be very difficult to identify and study because they are rare. The recent development of suitable methods to isolate and characterize cancer stem cells has thus provided a new impetus to the field of cancer research in general and breast cancer research in particular. A critical contribution has been the creation of mice that lack an immune system and thus can serve as long-term hosts for primary sources of malignant human cells. Another advance has been the development of methods for separating different subsets of cells without killing them, so they can then be tested for their ability to generate a tumour in a transplanted immunodeficient mouse. Cells containing tumour-initiating activity, dubbed 'cancer stem cells' have been found in a number of different human cancers, including leukemia (1994),

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breast cancer (2003), brain cancer (2004), prostate cancer (2005) and colon cancer (2006). Interestingly, there is now growing evidence that the cells that can generate new tumours are not necessarily normal stem cells that have become cancerous, but may represent "later" cell types that have reactivated stem cell properties. In addition, the situation in cancers is complicated by the fact that they are continuously evolving new subclones of more aggressive cells.

Breast cancer stem cells

As a pre-requisite to developing therapies targeted at cancer stem cells, many questions must first be answered. What is the molecular machinery that gives a cancer cell, "stem cell" properties? And what distinguishes cancer stem cells from the normal cells of the same tissue? What molecules and intracellular pathways can keep cancer stem cells quiet (non-dividing) but still alive, and which ones unleash their initiation of an uncontrolled proliferation activity? And how does the cancer stem cell genome affect the type of tumour that grows from it? These are just a few of the many questions being asked by researchers who are intent on finding strategies to target cancer stem cells effectively.

Ten years ago, researchers identified a small population of cells in a small group of patients' breast tumours that contained all of the cells that could produce new tumours when transplanted into mice that lack an immune system. These cells were positive for a cell surface protein called CD44 and were negative for another one called CD24. Since then, it has been shown that this population also contains the cells that are invasive. Using this selection strategy it may be possible to detect such cells even before a diagnosis of malignancy is given by conventional pathological methods used to diagnose the presence of a tumour. This is an example of one type of approach being developed for the earlier diagnosis of breast cancer cells. Identifying other breast cancer stem cell biomarkers that could provide immediate indicators of an adverse prognosis is also being widely pursued. Finding biomarkers is critical for mapping out the differentiation process, for distinguishing breast cancer stem cells from normal breast stem cells, and for providing possible targets for drug therapy. Breast cancer-specific biomarkers would also be a tremendous asset for the routine identification of breast cancer, predicting its prognosis, and diagnosing particularly aggressive forms of the disease.

Canadian contributions

In 1994, Canadian scientist John Dick with the University of Toronto and The Hospital for Sick Children identified a small population of tumour-initiating cells that could generate human leukemia in transplanted mice. This discovery prefaced the subsequent identification over the next decade of cancer stem cells in other types of solid tumours found throughout the body. Canadian scientists continue to invest considerable resources towards cancer stem cells, developing national and international research collaborations to facilitate ongoing studies. Canadian funding agencies have also recognized the importance of this research and in 2007 founded The Cancer Stem Cell Consortium which continues to promote cancer stem cell research today at home and abroad.

An important foundation of studies of human breast cancer stem cells are the creation of robust quantitative methods to characterize their normal counterparts. Connie Eaves from the Terry Fox Laboratory at the British Columbia Cancer Agency and University of British Columbia helped to initiate this field with a paper in Nature in 2006 that showed how mouse mammary stem cells could be detected and characterized as a biologically distinct subset of basal cells. Two years later, her group published a similar study in Nature Medicine providing the first method to detect human mammary stem cells also having a basal cell phenotype.

Advancing the genomics of breast cancer is the recent work from Sam Aparicio, a scientist also affiliated with the University of British Columbia and the British Columbia Cancer Agency. In collaboration with many colleagues, he published an initial landmark paper in Nature in 2009 and two more in 2012 – the first describing the changing genomic composition of a single breast cancer over time, the second detailing the DNA and RNA mutational architecture of 2000 breast tumours, and the third capturing the changing spectrum of DNA mutations in 104 patients with triple negative breast cancer. Taken together, this research provides the most advanced datasets on breast cancer, not only identifying new subgroups within the breast cancer population but also underscoring the molecular individuality within breast cancer populations. Being able to categorize breast cancers in this way creates a better picture of the disease and provides a new context for understanding why patients' responses to therapies may vary so greatly.

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Clinical studies

Clinical trials are being conducted to evaluate the importance of cancer stem cells in designing more effective treatments for breast cancer. For example, in a study sponsored by the National Cancer Institute, patients older than 16 years who are scheduled to have their cancers removed by surgery will have blood removed prior to the surgery or biopsy and also a sample of normal tissue removed when the cancer is excised. These tissues will be examined for the presence of cancer stem cells, and then over the next eight years, patients will be monitored via additional blood and/or bone marrow samples and imaging scans. Researchers are hoping that identifying cancer stem cells in tumour and/or normal tissue may enable the likelihood of recurrence to be predicted sooner than by current methods for tracking breast tumour growth.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) in the USA is also trying to use cancer stem cells as predictors of outcome. In this case, an ongoing clinical trial is evaluating whether the level of expression of potential cancer stem cell biomarkers (ALDH1 and HER2) can predict the response to adjuvant trastuzumab therapy in women with early stage breast cancer who had been previously treated in the NSABP B31 clinical trial. This 2-year trial is due to be completed in 2013. The outcome may help to identify changes that occur in DNA and biomarkers that correlate with breast cancer outcome.

Web Resources

Readers may wish to peruse the recommended sites below for more information about breast cancer and the application of stem cells for this disease.

- American Cancer Society: http://www.cancer.org/
- BC Cancer Agency: http://www.bccancer.bc.ca/default.htm
- Canadian Cancer Society: http://www.cancer.ca/
- Cancer Research UK: http://www.cancerresearchuk.org/
- National Cancer Institute: http://www.cancer.gov/cancertopics/types/breast