Breast Cancer Basics

cancer noun \ˈkæn(t)-sər\ : a malignant tumor of potentially unlimited growth that expands locally by invasion and systematically by metastasis

Before beginning our discussion about cancer of the breast, I want to give you some very basic information about cancer in general and how its unique characteristics compare to a normal cell.

Normal body cells can:

- Reproduce themselves EXACTLY
- Stop reproducing at the right moment
- Stick together in the correct place
- Self-destruct if a mistake occurs or they are damaged
- Mature and become specialized
- Die (they are programmed to do so), and when appropriate they are renewed by like cells
Cancer cells are different from normal cells in the following ways:

- Cancer cells don't stop reproducing
- Cancer cells don't obey signals from other cells
- Cancer cells don't stick together; they can break off and float away
- Cancer cells stay immature and don't specialize, so they become more and more primitive, and they reproduce quickly and haphazardly
- Cancers cells lose their programmed death pathway

In this chapter we are going to explore the nature of breast cancer. It is a mystery to us why the female breast is vulnerable to developing cancer. It may have something to do with monthly cycling of glandular cells, yet more than half of breast cancers develop in older women after the breast glands have come to rest. We know that cancer tends to occur in organs with cells that are constantly cycling through cell renewal. The replacement of a cell requires the production of a new set of genes, and this process can lead to mistakes (mutations) that the cell is unable to repair. The mistakes can then be repeated, causing a cell to grow according to a new blueprint in a process that is out of control, and this process results in cancer.

First, let's examine the anatomy of the female breast (Figure 1.1). The female breast is composed of milk-producing lobules connected to milk ducts that carry milk from the lobule to the nipple. There are at least twelve or more of these separate branching ductal-lobular units that occupy the four quadrants of the breast. Supporting and surrounding the glandular units are fibrous tissue, fat cells, blood vessels, and the lymphatic system that drains from the breast to the lymph nodes. We believe that the majority of breast cancers are due to a genetic mistake within the cells lining the lobules or ducts. There is evidence that genetic mistakes are common, and the majority are harmless. Cells actually have the ability to self-repair these genetic mistakes so that they do not go on to become cancer.

A cancer is born when a mistake occurs at a critical point in the
cell's genetic blueprint, or DNA, and it goes unrepaired. This genetic mistake affects the behavior and characteristics of the affected cell and the new cells that are produced. When a cell becomes genetically unstable, it has gone bad. These unstable cells continue to divide, passing along the damaged or mutant genetic message to the next generation of cells.

As the new cluster of cancer cells emerges from a milk duct or lobule in the breast, it can remain within the duct system (in situ), or it can invade the basement membrane and spread into the fat and supporting tissue (invasive or infiltrating). (See Figure 1.2.) This ability to grow and invade is a characteristic of cancer, and it can spread locally, within the breast, or spread into lymph and blood vessels.

The resulting group of cancerous cells (clone) can have most of the same characteristics as the normal breast duct cell (i.e., hormone receptors) and grow slowly but steadily. On the other hand, the mutation(s)
can lead to a clone that is highly malignant, with the resulting cells having no resemblance to the normal breast cells. We are beginning to understand that not all breast cancers are alike; they behave differently depending on the type of mutation and the resulting proteins or lack of proteins that direct the cell's behavior.

We now have the ability to analyze genetic material within cancer cells and map the unique patterns. From this research a new method of classifying breast cancer has emerged (see the discussion in chapter 3).

Breast cancers can remain contained within the duct system (in situ) for months or even years. Some cancers may require an additional mistake (mutation) to invade into the surrounding tissue. Other cancers probably immediately invade the surrounding tissue with the initial mutation. Cancers that remain in the duct system are called ductal carcinoma in situ (DCIS). (We discuss these preinvasive cancers in chapter 5.) If we can discover a DCIS before it invades the sur-

![Figure 1.2](image-url)

**Figure 1.2**
In situ and invasive ductal cancer
rounding tissue, there is no risk of its spreading to the body, and the cancer is highly curable with local treatment measures.

The rate of growth of a cancer varies considerably and is very dependent on the mutation that has occurred. Some breast cancers retain the ability to be influenced by hormones (estrogen), and the presence or lack of estrogen will influence their growth.

The genetic blueprint (DNA) within a cancer cell is unstable, and with continued growth further mutations occur. Some of these mutations are so unstable that they become lethal to the cell population itself, thus ending the cancer growth. We tend to think of cancers as “strong” rogue cells. In reality many cancer cells, especially the most malignant, are fragile and just hanging on. Current treatments are able to take advantage of this fragile state, and in the future treatments will target this vulnerability.

As stated earlier, the rate of growth of breast cancer cells varies considerably. The slower growing cancers of the Luminal A type (see chapter 3) take six or more months to double in size (Figure 1.3), while the triple-negative (basal cell) cancers can double in size in just one to two months. The ability to spread into the lymph system and bloodstream depends on the underlying DNA mutation and the size of the cancer. Most cancers cannot spread into lymph and blood vessels (metastasis) until they exceed about 1 centimeter (10 mm) in size (Figure 1.4). We believe that over time slower-growing cancers can further

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**Figure 1.3**

Growth of cancer cells over time
mutate and increase their growth rate, potential to spread, and degree of malignancy.

Once a cancer has become invasive, there is risk of its spreading into the lymphatic system and the bloodstream. We are not sure what mechanism a cancer cell uses to invade vessels, but it is thought that the process requires DNA programming or mutation. Women often ask if a needle biopsy can disrupt cells and cause them to spread into the lymph nodes. I think this can occur, and in some cases we do see isolated tumor cells shortly after biopsy in the first lymph node that drains the breast. But we also know these women have the same outcome as women without the presence of isolated tumor cells in their lymph nodes. Evidence suggests that the spread to the lymph by the trauma of the biopsy is not associated with true cancer cell metastasis and does not lead to a decrease in cure rates.

The needle-directed biopsy of a cancer is the standard for diagnosis of breast cancer. From this small core of tissue, about the size of a pencil lead, the type of breast cancer can be determined, allowing the treat-

![Figure 1.4](image-url)
ment team to plan therapy most appropriate for the patient. (We discuss the analysis of tumor tissue more completely in chapter 4.)

In the past we placed huge importance in staging a cancer on analysis of the draining lymph nodes, looking for spread of tumor cells and extent of the spread. Figure 1.5 demonstrates the distribution of lymph nodes draining the breast. Until a few years ago surgeons would remove a majority of the lymph nodes at the time of the breast cancer surgery. Spread to lymph nodes is an important factor to determine your prognosis (probable course or outcome of the disease), but it is no longer necessary to do extensive lymph node surgery. There is increased risk of lymphedema (arm swelling) that does not justify the information gained through removal of the majority of nodes. Instead, by removing
the sentinel node (the first draining lymph node; see chapter 6), we can obtain the needed information without the risks of more extensive surgery. If there is extensive lymph node involvement at the time of diagnosis, the involved lymph nodes are usually treated with systemic therapy, followed by radiation and in some cases surgery.

Historically, lymph node involvement was the strongest predictor of risk of spread into the bloodstream. This is changing. Using a number of tests that can be performed on the needle biopsy, we have greatly improved our ability to assess the risk of cancer spread. (This topic is discussed further in chapters 4 and 6.)

It is important to treat cancer in the lymph nodes draining from the breast. By using sentinel lymph node sampling, ultrasound, and other imaging techniques such as MRI and PET scans, we can plan approaches that use combined therapies for those women whose cancer has spread to the lymph nodes. For the majority of women with no lymph node involvement or microscopic involvement, we can avoid extensive and potentially damaging lymph node surgery. A number of clinical trials have demonstrated that full lymph node removal does not improve survival rates.

The most serious and dangerous event is when cells invade into the blood vessels and metastasize into the body. We call this occurrence systemic spread. Current technology does not allow us to detect early systemic disease because imaging tests are not sensitive enough to find microscopic cells within the body. A number of researchers are examining ways to detect cancer cells circulating in the blood by using special antibody preparations. This line of inquiry is very promising for the future, although more work needs to be done to ensure development of a test that is consistently accurate, reliable, and meaningful.

Once invasion has occurred and the cancer has grown to about 1 centimeter, it can attract and produce blood vessels (angiogenesis) that allow it to break off (metastasize) and spread into the lymph and blood system (systemic spread). In this critical process, the cancer cells produce protein messengers known as vascular endothelial growth factors.
(VegF). To counteract the effects of VegF, researchers have developed a number of antibodies and molecules that can reduce or prevent angiogenesis and ultimately lead to the destruction of the cancer.

With new technologies such as reverse transcription-polymerase chain reaction (RT-PCR), researchers are able to compare the genetic blueprint of a normal cell to the transformed malignant cell and identify the abnormal mutant genes. Identification of abnormal gene patterns has led to a new classification (typing) system for breast cancer that will be discussed in chapter 3. This ability to analyze the mutant genes has also led to the recognition that certain of the abnormalities are related to cancer cell functions such as invasion, proliferation (cell growth), angiogenesis, and metastasis.

Using these techniques, commercial laboratories have been able to analyze cancer cells for the presence of mutant genes associated with systemic spread and to develop tests that can predict how likely a cancer is to recur or metastasize. Several of these prognostic (predictors) tests have been developed by two labs: Genomic Health in Northern California, which has a twenty-one-gene test called Oncotype DX; and Agendia in Irvine, California, which has a seventy-gene test known as MammaPrint. Both tests help the cancer specialist to select those women who may benefit from systemic therapies.

Based on the identification of gene mutations, it is now possible to develop therapies targeted at the specific mutations; these therapies can reverse the effects of these mutations and potentially reverse the malignant process. In the previous edition of this book, I alluded to this possibility, which has now become a reality.