BREAST CANCER Prevention INSTITUTE
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BCPI FACT SHEET

# Breast Cancer Formation

## *Cancer formation and breast cell growth*

Cells grow through mitosis, or cell division. Before a single cell divides into two cells, it must make a complete copy of its DNA. The process of cell division occurs during the cell cycle, which also includes a resting phase after the synthesis of new DNA and other cell structures; thus, if errors are made when DNA is copied, they can be repaired during this resting phase.

***Table 2: Lobular Morphology, Cancer Vulnerability, and Structure***

| Type of lobule | Morphology of lobules | Type of cancer that forms from lobules | Structural and metabolic differences of lobules |
|---|---|---|---|
| Type 1 | Average 11 ductules per lobular unit | Ductal cancers (which are approximately 85 percent of all breast cancers), arising in milk ducts[33] | • Highest number of estrogen and progesterone receptors in the cells<br>• Highest rate of cell proliferation (marked by Ki67 protein)<br>• Shortest DNA doubling Time |
| Type 2 | Average 47 ductules per lobular unit | Lobular cancers (which are approximately 15 percent of all breast cancers), arising in milk glands | • Approximately half the number of estrogen and progesterone receptors as Type 1 lobules<br>• One third of the cell proliferation marker Ki67 protein of Type 1 lobules<br>• A shorter DNA doubling time than Type 3 lobules |
| Type 3 | Average 81 ductules per lobular unit | Cancer-resistant | • Negligible numbers of estrogen and progesterone receptors<br>• Less than one tenth of the cell proliferation marker Ki67 protein of Type 1 and Type 2 lobules<br>• Type 4 lobules regress to Type 3 after cessation of breastfeeding |
| Type 4 | Average 81 ductules per lobular unit | Cancer-resistant | • Absence of proliferation[34]<br>• Lobules produce and contain colostrum (early milk) or mature milk in their glands |

### *Cancer formation*

The time that mitosis (splitting from one into two cells) and DNA synthesis take is the cell's doubling time. The cells of each type of lobule have different doubling times and other measures of metabolic activity, such as cellular proliferation (identified by the level of the Ki67 protein it contains).[35] A short doubling time may result in more mutations, because the cell has a shorter resting phase (i.e., a shorter time for DNA repair). Cancer develops from a mutation or damage done to a cell's DNA.

Genotoxins (such as radiation or some chemicals) can directly damage DNA and cause a mutation without cell division. Unless the mutation occurs in a critical gene (such as p53, a tumor suppressor gene which normally detects mutations in DNA at the G1 checkpoint, and in which a mutation permits many cancer-producing mutations to pass the G1 checkpoint unchanged), most cancers form after several mutations have built up in a cell over a number of years. After mitosis, any mutated daughter cells will undergo mitosis again with a greater chance of more mutations forming.

### *Lobules' cancer vulnerability*

The shorter the time in which the DNA doubles, or copies itself, the greater is the risk of forming a mutation or cancer cell. Type 1 and Type 2 lobules copy their DNA more quickly than Type 3 lobules, so they are more cancer-vulnerable. Again, when DNA is copied quickly and the cell cycle is shorter, there is less time in the resting phase (when DNA mistakes are repaired), so more mutations are passed on. There is not enough time to repair all of them before the cell divides.

Eighty-five percent of breast cancers arise in Type 1 lobules (ductal cancers). Ten to 15 percent of all breast cancers arise in Type 2 lobules (lobular cancers). Almost all cancers arise in Type 1 and Type 2 lobules.

Estrogen and progesterone production stimulates this DNA reproduction and cell growth. As noted earlier, Type 1 lobules have the most estrogen and progesterone receptors, and Type 2 lobules have fewer than Type 1. Type 3 lobules have negligible numbers of estrogen and progesterone receptors. The differing quantities of receptors in the lobules' cells' nuclei correspond to levels of cell proliferation.

### *Cancer detection*

A breast cell's doubling time accounts for the time a tumor takes to become large enough to be clinically detectable through an imaging study, such as a mammogram, or by a physical exam through palpation, or feeling the breast. On average, one microscopic breast cancer cell takes eight to 10 years to grow through mitosis into a tumor mass (lump) one centimeter in diameter.[36] This is why cancer caused by an induced abortion[37] may not become detectable for eight to 10 years.

### *Types of cancer*

There are invasive and *in situ* cancers of both the milk ducts and milk glands. This classification depends upon the origin and location of the cancer cells. The receptors of the cancer cells are also examined and reflect their genetic phenotype.

When cancer cells form in the milk ducts or glands but do not penetrate the outer layer of the duct or gland (the basement membrane), a cancer is said to be an *in situ* cancer. Less than half of these ductal *in situ* cancers can be felt as a "lump," but 90 percent are detected by mammographic calcifications.[38] These cancers are curable, because they have not penetrated the basement membrane where the lymphatic channels or blood vessels are located; they cannot spread to other parts of the body. *In situ* cancers can develop in the milk duct and form ductal carcinomas *in situ*. They may also arise in the milk glands and form lobular carcinomas *in situ*.

Invasive cancers have penetrated the basement membrane and can spread throughout the body, becoming metastatic and life-threatening. Most invasive cancers start as *in situ* cancers, and most (85 percent) of these are ductal cancers.

Breast cancer treatment has become more effective by routinely analyzing the cancer cells for estrogen (ER), progesterone (PR), and Her 2 neu (HER2) receptors. These receptors can be positive (+) or negative (-). They are also assessed by how proliferative the cells are by measuring the protein Ki67.

Breast cancers are sometimes described by the array of genes that are expressed. At present there are four major subtypes: luminal A (ER+ and/or PR+, HER2-, low Ki67), luminal B (ER+ and/or PR+, HER2+ or HER2- with high Ki67), triple-negative/basal-like (ER-, PR-, HER2-), and HER2 type (ER-, PR-, HER2+).

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**REFERENCES**

[33] A lobule has a milk duct and glands. The gland makes the milk, and the milk duct collects the milk. Under the microscope, pathologists can determine whether cancer is ductal or lobular carcinoma. Ductal cancers start in the ducts of Type 1 lobules and lobular cancer start in the glands of Type 2 lobules.

[34] Type 4 lobules do not proliferate, as they are terminally differentiated and producing milk.

[35] R. Dickson and J. Russo, Chapter 2: "Biochemical Control of Breast Development," in *Diseases of the Breast*, eds. Jay R. Harris, Marc E. Lippman, Monica Morrow, and C. Kent Osborne, 2nd ed. (Philadelphia: Lippincott Williams & Wilkens, 2000), 16-18.

[36] J. Gershon-Cohen, S.M. Berger, and Herbert S. Klickstein, "Roentgenography of breast cancer moderating concept of 'biologic predeterminism,'" *Cancer* 16, no. 8 (August 1963): 961-964.

[37] An examination of the timing in which breast cancer is statistically most likely to manifest itself after a woman obtains an induced abortion (around a decade to 14 years thereafter, with a seemingly diminished risk of manifestation 15 or more years after the abortion is procured) seems to indicate that induced abortion is itself a carcinogenic experience and is not merely an event that weakens a woman's defenses against breast cancer. See Appendix E for further explanation.

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