Breast Cancer and Environmental Risk Factors

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FACT SHEET #5

Q & A's from the Cornell University Program on Breast Cancer and Environmental Risk Factors in New York State

The Biology of Breast Cancer

To reduce cancer risk, we first need to understand how cancer develops in the body. Understanding how cancer develops can help us find ways to slow down its progress or perhaps stop it from occurring in the first place. For example, understanding that breast tissue of girls and young women is especially sensitive to cancer causing agents can help direct risk reduction efforts to these groups. Making sense of cancer means taking a step toward more informed decisions about our bodies, our selves, and our environment.

How Does (Breast) Cancer Develop?

Cancer develops through a multistep process in which normal, healthy cells in the body go through stages that eventually change them to abnormal cells that multiply out of control. In most cases, cancer takes many years to develop.

Normal cells in the body communicate with each other and regulate each other's proliferation (division). Cells proliferate to replace worn-out cells. When cancer occurs, cells escape the normal controls on their growth and proliferation. This escape from control can happen through a variety of pathways.

Part of the multistep process to cancer includes acquiring damage (*mutations*) to genes that normally regulate cell proliferation. A series of permanent mutations in *tumor suppressor genes* and *proto-oncogenes* (see p. 4) are needed before cancer develops. Buildup of damage in these genes can result in uncontrolled cell proliferation. In some cases, further damage can lead to cells that can break away from the primary tumor and form cancers at other sites in the body (*metastasis*).

Breast tissue is particularly sensitive to developing cancer for several reasons. The female hormone estrogen stimulates breast cell division. This division can increase the risk of making damage to DNA permanent. Furthermore, breast cells are not fully matured in girls and young women who have not had their first full-term pregnancy. Breast cells that are not fully mature bind *carcinogens* (cancer causing agents) more strongly and are not as efficient at repairing DNA damage as mature breast cells.

How Do Things Go Wrong?

When cancer develops it is because things go wrong in the cells of the body. In the breast tissue of young women and girls, cells are especially sensitive to DNA damage from cancer causing agents.

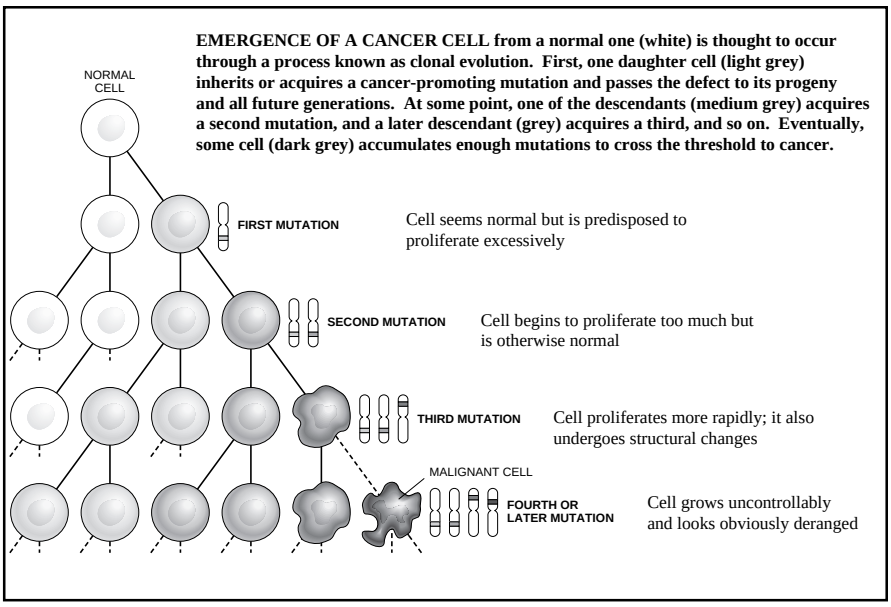
Mutations in DNA

In every one of the trillions of cells in the body, there is an "operations manual" made up of DNA molecules. The information in the manual is separated into chapters, called *genes* which are made up of small units of DNA. Genes are written in a DNA code that must be transcribed and translated in order for the cell to make the protein signals specified in each gene. These proteins are signals which tell the cell how to function.

A change in the genetic code is a *mutation*. Mutations can happen by subtracting from, adding to, or rearranging the original code. Mutations can happen randomly within the cell's DNA, but they can also be induced. A substance that causes mutations in DNA is called a *mutagen*. Mutations in a gene may interfere with its ability to make a functional signal, or cause it to code for a protein that sends an incorrect signal to the cell.

Most mutations are repaired by the cell, but in rare cases mutations do not get repaired. If a mutation is not repaired before a cell copies its DNA and divides into two cells, then the mutation is passed on to the two new *daughter* cells and becomes permanent. Rare genetic disorders (e.g., Ataxia Telangiectasia) are one way that cells are deprived of the ability to repair DNA, and may experience buildup of mutations in cells.

Mutations in most of a cell's DNA have no effect on whether the cell will become cancerous. However, the protein signals coded by



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a very small proportion of the total genes in each cell regulate cell growth and division. These regulatory genes include the two groups of genes called *proto-oncogenes* and *tumor suppressor genes*. A series of mutations in the DNA of either and/or both groups of these growth controlling genes can eventually lead to cancer. Buildup of these mutations may take years to develop.

Breast Biology and Susceptibility to Cancer

Cells that divide are at a higher risk of acquiring mutations than cells that don't divide. Cancer is generally rare in tissues in which cells don't divide, like nerve tissue. Alternatively, cancer is more common in tissues in which cells divide frequently such as with breast, skin, colon, and uterine tissues.

Young women and girls have breast tissue that is especially sensitive to cancer causing agents (*carcinogens*). Unlike other tissues in the body like the liver and heart that are formed at birth, breast tissue in newborns consists only of a tiny duct. At puberty, in response to hormones (like estrogen that is secreted by the ovary), the breast duct grows rapidly into a tree-like structure composed of many ducts. Most breast development occurs between puberty and a woman's first pregnancy. The immature breast cells, called "stem cells", divide rapidly during puberty. The cells in the immature, developing breast are not very efficient at repairing mutations, and they are more likely to bind carcinogens.

Therefore it is important to reduce the exposure of young women and girls to carcinogens that might damage DNA during this phase of rapid breast development. For example, Japanese infants and young women exposed to ionizing radiation from atomic bombing during WWII have high rates of breast cancer as adults. It is also important to reduce exposure to environmental estrogens during these critical times. Environmental estrogens (estrogen 'mimics') are synthetic chemicals that can act like human estrogen in a woman's body, and may stimulate cell division in the breast.

After a woman's first full-term pregnancy, hormonal influences transform a high proportion of her breast cells into mature, *differentiated* cells which make milk. Milk producing cells are fully mature and less sensitive to DNA damage than immature *undifferentiated* cells. Therefore, susceptibility to mutations declines in the breast cells of women who have had an early full-term pregnancy. Some evidence also suggests that breast feeding further reduces the breast cells' sensitivity to mutations.

Though much of what we know about the biology of breast tissue susceptibility to cancer is based on research in animals, it is believed most of this knowledge can be applied to human biology.

CRITICAL PERIODS OF SUSCEPTIBILITY:

- *Birth to 4 years*
- *Puberty*
- *End of Puberty to 1st full-term pregnancy*

Biological Characteristics of Critical Periods

- ** Rapid cell division*
- ** Breast cells have higher proportion of "stem cells"*
- ** Mutations can be passed on if not repaired*
- ** Stem cells are more susceptible to carcinogens*

AFTER 1ST FULL-TERM PREGNANCY:

Biological Characteristics AFTER Critical Periods

- ** Fewer stem cells*
- ** Less cell division*
- ** More cells are differentiated*
- ** Differentiated cells repair DNA more efficiently*
- ** Differentiated cells bind carcinogens more weakly than stem cells*

Original hypothesis and animal modeling done by Drs. Irma and Jose Russo

The Stages of Tumor Development

Cancer develops through different stages. These stages may or may not eventually lead to invasive and metastatic cancer. In most cases it takes many years for cancer to develop. Early detection of any tumor is important because it increases the chances of removing the cancer before it becomes life-threatening.

Normal: There are trillions of cells in the healthy human body. Even though adults stop growing, the body constantly replaces worn-out cells with new ones to stay healthy. Cells must communicate and respond to each other's checks and balances to maintain the correct number of healthy cells.

Genetically altered cell(s): Tumor development begins when at least one cell has a genetic mutation (mistake in DNA) which causes it to divide and proliferate when it normally would not. This leads to more cells with the same mistake.

Hyperplasia: Cells look normal but grow too much. Further damage can lead to "dysplasia."

Dysplasia: Cells proliferate too much AND look abnormal in shape and orientation. Cells are less responsive to surrounding cells and the body's signals to stop proliferating. Further damage and/or cell changes can lead to "in situ" (pronounced "in-SIGH-two") cancer.

Atypia: Cells look abnormal. Atypia is a general term describing how cells *look*. For example, one cell can appear atypical, but a group of cells display "dysplasia."

Benign tumor (not life-threatening): Although cells are not normal, they do not have the ability to travel to other parts of the body. Cells in benign tumors are typically more differentiated (mature) and organized than cells in cancerous tumors. In some cases a benign tumor may eventually become an invasive or metastatic tumor.

In situ carcinoma (cancer): Cells become even more abnormal in growth and appearance but the tumor cells have not broken through the boundary around the tumor that separates it from surrounding tissues. This boundary is like a capsule that contains the tumor. Cells may acquire additional damage and/or changes which can lead to invasive cancer.

Invasive cancer (can be life-threatening — *primary tumor*): The uncontrolled growth of cells in the tumor allow some cells to break through the capsule-like boundary and invade nearby tissues. Generally, invasive tumors are life-threatening if the cancer cells are present within a vital organ like the kidneys, lungs, or liver. Invasive tumors in non-vital organs like the breasts are not necessarily life-threatening unless they become *malignant* and migrate to a vital organ. Therefore, early detection of any tumor is important because it increases the chances of removing the cancer before it becomes life-threatening.

•Malignant: Cells from the invasive (primary) tumor gain the ability to enter the blood stream or lymphatic system and to travel to distant areas in the body (metastasize).

Metastatic cancer (life-threatening — *secondary tumors* that come from the primary invasive tumor). Cells from the malignant primary tumor gain the ability to re-establish somewhere else in the body where they form new cancerous tumors. The secondary tumors are called *metastases*. Metastatic tumors can become fatal because they may disrupt the function of vital organs.

Where Can Things Go Wrong?

Cells in the body are regulated through the cell cycle. Damaged cells may eventually become deaf to normal regulation and multiply out of control.

Cell cycle

Even though adults are no longer growing, many cells in an adult's body continue to divide to replace worn out cells. To divide, a cell must enter a "highway" called the cell cycle. There are specific signals that tell a cell when to enter the cell cycle and how long to stay there and divide. For example, *cyclins* are molecules that help control the cell cycle. There are also signals which tell the cell when to exit the cell cycle. When a cell divides, it copies its DNA and produces two new daughter cells. If any of the signals controlling the cell cycle fail, cell division may go unchecked.

Figure created by Dr. Roy Levine

The female hormone estrogen is one signal that tells certain kinds of breast cells to enter the cell cycle. This leads to increased cell division. In addition, researchers suspect an interaction between estrogen and certain cyclins (e.g. *cyclin-D1*) which stimulates the cell cycle.

Factors that are locally produced by breast cells can also affect cell division. One example is the growth factor TGF-alpha (transforming growth factor alpha). Researchers have shown that over-expression of TGF-alpha is associated with increased cell division in breast cells, and hence may be associated with breast tumor progression (see Stages of Tumor Development). Over-expression of growth factors may be related to damage in *proto-oncogenes* (see below).

Proto-oncogenes and oncogenes: "Go" genes

Proto-oncogenes are normal genes that code for the "go" signals controlling the cell cycle. These signals tell a cell to enter the cell cycle and code for how long it should stay there and divide. If a proto-oncogene loses the ability to regulate the cell cycle, the cell may reproduce uncontrollably because it stays in the cell cycle and continues to divide. A mutated proto-oncogene that has lost control of its "go" signal is called an *oncogene*.

Oncogenes code for protein signals that stimulate the cell to enter or continue in the cell cycle. This leads to inappropriate cell division and growth of a developing tumor. For example, a mutation in a proto-oncogene may cause the over expression of certain growth factors, and lead to inappropriate division of cells. That is why some growth factors are seen at higher levels in many breast tumors.

Another example is the *erb-B2* receptor gene, an oncogene which codes for a receptor protein. The receptor in normal cells must be bound to a certain growth factor before it can stimulate the cell to enter the cell cycle and divide. But in faulty versions of the *erb-B2* receptor gene, the receptors specified by this gene can release a flood of signals to stimulate increased cell division without being bound to the growth factor. Researchers have shown that up to 30% of primary breast cancers have too many copies of the *erb-B2* gene.

Other oncogenes that researchers have found to be related to breast cancer include the tyrosine kinase family of growth factor receptors, the *c-myc* oncogene, cyclin *D-1*, and the cyclin regulator, *CDK-1*.

Tumor suppressor genes: "Stop" genes

Just as the cell has "go" signals that tell it when to enter the cell cycle, it also has genes which control the "brakes." Cells with tumor suppressor genes that are mutated or inactivated lose control over their brakes. Brakes are important in the cell cycle. Putting on brakes at certain "check points," allows the cell to check for any damage in its DNA. Repairs must be made before the cell is allowed to go on in the cycle. Without these brakes, cells with damaged DNA would copy the mutations, divide, and pass on the damage to daughter cells. The damage is then established as a permanent mutation in subsequent generations of new cells. Therefore, an important function of tumor suppressor genes is to maintain the integrity of the DNA in cells.

An example of a vital tumor suppressor ("stop") gene is the p53 gene. A mutation in the p53 gene is the most common genetic change found in breast cancer. One function of this gene is to keep cells with damaged DNA from entering the cell cycle. The p53 gene can tell a normal cell with DNA damage to stop proliferating and repair the damage. In cancer cells, p53 recognizes damaged DNA and tells the cell to "commit suicide" (*apoptosis*). If the p53 gene is damaged and loses its function, cells with damaged DNA continue to reproduce when normally they would have been removed through apoptosis. This is why the p53 gene has been termed "The Guardian of the Genome."

A small proportion of breast cancer cases (5%) are related to the inheritance of susceptibility genes. Alterations of the recently discovered "breast cancer susceptibility genes," BRCA 1 & 2, are involved in some inherited cases of breast cancer. If inactivated, these tumor suppressor genes can act indirectly in the cell by disrupting DNA repair. This allows the cell to accumulate DNA damage, including mutations that can encourage cancer development.

Other tumor suppressor genes that researchers have found may be related to breast cancer include the *Retino blastoma*, *Brush-1*, *Maspin*, *nm23*, and the *TSG101* genes.

Cell adhesion proteins

Healthy cells in the body are contained in a very orderly arrangement, like cobblestones in a street. Cobblestones are cemented in position and are contained by a curb. Like cobblestones, cells are cemented in position by *cell adhesion proteins* and are contained in their proper location by a curb called the *basement membrane*. In order for cells that have become cancerous to metastasize, the cells have to "break through" the basement membrane and enter the blood stream or lymphatic system.

Certain genes code for molecules which signal the cell to make cell adhesion proteins. If these genes are damaged by mutations the resulting adhesion protein may no longer function properly. Without the cell adhesion proteins, cells do not stick as strongly to each other and to the basement membrane. The cells themselves may no longer stay in their orderly arrangement and may escape the boundaries of the basement membrane. Researchers have shown that expression of normally functioning adhesion molecules is progressively reduced in more advanced tumors. Two types of cell adhesion protein that researchers have found to be related to breast cancer are the *cadherins* and *integrins*.

Early detection of tumors is vitally important because damage to the genes governing cell adhesion molecules can be one of the life-threatening stages of tumor progression. Removing a tumor when it is still contained and before cells have escaped the confines of the original tumor reduces the chance that cells may have metastasized and generated new tumors in other areas of the body.

Summary

- Cancer is a multistep process in which normal, healthy cells in the body go through stages that eventually change them to abnormal cells that multiply out of control. In most cases, cancer takes many years to develop.

- Breast tissue can be sensitive to developing cancer. The female hormone estrogen stimulates breast cell division, which can increase the risk of breast cancer. Furthermore, breast cells are not fully mature in girls and young women who have not had their first full-term pregnancy. Breast cells which are not fully mature bind carcinogens more strongly than and are not as efficient at repairing DNA damage as mature breast cells. Therefore, it is very important to reduce exposure to cancer causing agents during the critical periods in a woman's life.

- Part of the multistep process to cancer includes buildup of mutations to genes that normally regulate cell division. Damage to tumor suppressor genes and/or proto-oncogenes can eventually cause cancer. Damage to genes that code for cell adhesion proteins can lead to cells that can break away from the primary tumor and form cancers at other sites in the body.

- Development of invasive and metastatic cancer is a multi-step process. Early detection of tumors is vitally important. Removing a tumor before cells can escape the confines of the original tumor reduces the chance that cells will metastasize and generate new tumors in other areas of the body.

- Taking steps to reduce risk includes understanding cancer and making more informed decisions about our bodies, our selves, and our environment.

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A complete bibliography is also available at http://www.cfe.cornell.edu/bcerf/

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