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FACT SHEET #9

Breast Cancer and Environmental Risk Factors

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

Estrogen and Breast Cancer Risk: What Is The Relationship?

Estrogen is a hormone that is essential for the normal growth and development of the breast and tissues important for reproduction. It is important for childbearing and helps regulate a woman's menstrual cycles. It also helps maintain healthy bones and the heart. However, lifetime exposure to estrogen is also associated with increasing a woman's risk for breast cancer. Understanding how estrogen works in the body may help women to make more informed decisions about their bodies and their health.

What is estrogen?

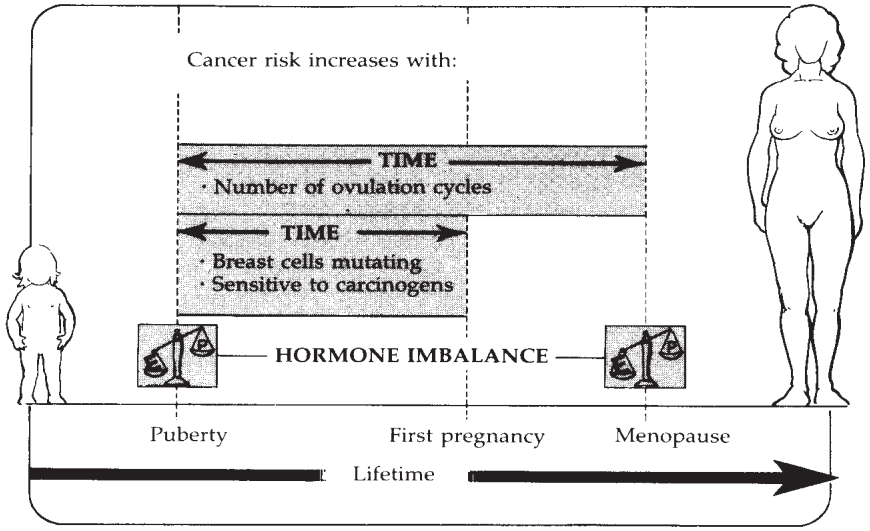
Estrogen is a hormone that is a chemical messenger in the body. It is important for normal sexual development and is essential for the normal functioning of the female organs needed for childbearing such as the ovaries and uterus. Estrogen helps control a woman's menstrual cycle. It is important for the normal development of the breast. It also helps maintain healthy bones and the heart. All of these are *estrogen target tissues*-organs or tissues that estrogen can influence. During the childbearing years from puberty to menopause, organs called the ovaries produce estrogen. After menopause, when the ovaries no longer make estrogen, body fat is the primary source for estrogen made by the body.

What are some clues that suggest estrogen is related to breast cancer risk?

The effect of ovarian hormones like estrogen on breast cancer risk was first shown over 100 years ago when researchers found that removing the ovaries of women with breast cancer improved their chances of survival. Recent studies have shown that women who had their ovaries removed early in life have a very low incidence of breast cancer. Similarly, rats and mice whose ovaries have been removed develop few if any breast tumors. Men, who do not have ovaries and have low blood levels of estrogen, have low breast cancer rates compared to women.

Recently many researchers have examined the possible relationship between exposure to estrogen and breast cancer risk. One recent study showed that women who developed breast cancer tended to have higher levels of estrogen circulating in their bodies than women without breast cancer. Another recent study showed that women who had been treated for breast cancer, and who had higher levels of estrogen in their bodies, had a return of the disease sooner than women treated for breast cancer and who had lower levels of estrogen.

This evidence suggests that life-long exposure to estrogen, and perhaps to other ovarian hormones, plays an important role in determining breast cancer risk. Studies that have identified risk factors for breast cancer have found that women who experience menarche at an early age (when a girl gets her first menstrual period), or menopause at a later age (when a woman's periods end) have a higher risk of breast cancer. This also supports the theory that the number of menstrual cycles a woman has, and hence the length of exposure to estrogen during her lifetime, affects her risk for breast cancer.



Dr. S. Love, DR SUSAN LOVE'S BREAST BOOK, SECOND EDITION, FULLY REVISED, (figure 41-5 page 193). © 1995 Susan M. Love, M.D. Reprinted by permission of Addison Wesley Longman.

How does estrogen work?

As a messenger: During each menstrual cycle, estrogen together with other ovarian hormones signals cells in the breast to divide and multiply. Estrogen also signals the cells of the uterus to divide. How does estrogen make and deliver this "message" to divide? Other hormones signal the ovaries to make estrogen, and then the ovaries secrete estrogen into the bloodstream. Estrogen travels through the blood, but only the cells in *estrogen target tissues*, like the breast and uterus, can recognize and use estrogen because they have *estrogen receptors*.

As a key in a lock: Estrogen has a shape that allows it to fit into an estrogen receptor in the same way a *key* fits into a "lock." The estrogen and the estrogen receptor bind to form a unit that enters the nucleus of the cell. The *estrogen-receptor unit* binds to specific regulatory sites on the cell's DNA (DNA is a cell's inherited genetic code), and this begins a series of events that turns on estrogen-responsive genes (genes are the functional units of DNA that control and direct the activities of a cell, such as cell division). These specialized genes instruct the cell to make proteins that signal the cell to carry out important activities. Some of these signaling proteins can tell the cell to divide.

As different versions of the same key: Estrogen is present in the body in different forms. The estrogen receptor can bind with these different forms of estrogen--much like when one lock can be opened by more than one key. Some forms of estrogen are stronger than others. Stronger forms are more likely to initiate cell division than weaker forms. In addition, some forms of estrogen stay in the body longer than others.

How might estrogen affect the development of breast cancer?

Cell division and the cancer process: One characteristic of a cancer cell is that it multiplies out of control. The progression from a normal cell to a cancer cell is a multistep process that includes the build-up of damage to the DNA in key genes that control cell division.

Damage to a gene in DNA is called a *mutation*. This damage may happen in several different ways. Rarely, a child may inherit a mutated gene from a parent. For example, the breast cancer genes BRCA1 and BRCA2 may have mutations that parents can pass on to children. More commonly, a chemical or radiation that damages the DNA may cause mutations. Another cause of DNA damage is when a mutation arises by chance. The chance mutation is a result of the cell making a mistake in copying its DNA during cell division.

Since estrogen stimulates cell division, it can increase the chance of making a DNA copying error in a dividing breast cell. Estrogen can also have the effect of making a spontaneous or chemically-induced mutation permanent, since it influences the rate of cell division. Because mistakes in DNA become permanent if the cell divides and passes on the mutation, estrogen-stimulated cell division can increase the chance of making a mutation permanent.

The critical periods of breast growth and development: The breast is unique because unlike other organs (such as the liver) that are fully formed at birth, the breast in the newborn girl consists of only a few tiny ducts. During puberty,

estrogen from the ovaries stimulates immature breast cells, called *stem cells*, to rapidly divide and multiply to form a tree-like structure composed of many ducts.

Stimulating the development of the breast ducts is an important normal function of estrogen. However, immature breast cells are particularly sensitive to the effects of cancer-causing agents, called *carcinogens*. Animal studies have shown that rapidly dividing, immature cells of the developing breast are more likely to bind carcinogens. The immature stem cells are also less efficient at repairing damage to DNA caused by carcinogens. Stages when immature breast cells are particularly vulnerable to damage by carcinogens include 0-4 years of age, and from puberty to a woman's first full term pregnancy. During pregnancy, breast cells undergo changes that protect them against damage caused by carcinogens.

Effects on other hormones that stimulate cell division: Estrogen can indirectly stimulate cell division by instructing a target cell to make receptors for other hormones that stimulate breast cells to divide. For instance, estrogen affects the receptor levels of a female hormone called progesterone. In the breast, progesterone also acts as a chemical messenger that tells breast cells to divide. Estrogen may affect how the cell responds to "local" hormones called growth factors which also play a role in breast cell division. So, by affecting the level of other hormone receptors or growth factors, estrogen can indirectly stimulate cell division in the breast.

Support of the growth of estrogen responsive tumors: About one to two-thirds of all breast tumors have estrogen receptors and depend on estrogen for growth. That is why doctors often prescribe the *anti-estrogen* Tamoxifen for women who have *estrogen-receptor positive* breast tumors. Anti-estrogens can block the binding of estrogen to its receptor, and thereby prevent estrogen from delivering its message to the breast tumor cells to divide and multiply. Also, women who have a first full-term pregnancy late in life may be at increased risk for developing breast cancer. This is because by the time they get pregnant estrogen-responsive breast tumor cells may have formed, and the high levels of estrogen secreted during pregnancy may promote growth of the estrogen-responsive breast tumor cells.

Direct effect on breast cancer: Until recently, researchers thought that estrogen had only an indirect effect on breast cancer through its role in stimulating cell division and supporting estrogen-dependent tumor growth. New research is exploring whether the body's estrogen or synthetic estrogens can have a more direct effect in causing changes in cells that may lead to cancer in the breast and other body organs.

What might affect levels of estrogen in a woman's body?

Researchers are examining a variety of different factors that may enhance or reduce a woman's exposure to estrogen. These include lifestyle factors like diet, body fat, alcohol consumption, hormone replacement therapy, birth control, and exercise. Researchers are also examining whether environmental factors may affect a woman's exposure to estrogen, including exposure to chemicals that act like estrogen in a woman's body and to chemicals that disrupt the way estrogen works in a woman's body. The BCERF fact sheet *Estrogen and Breast Cancer Risk: What Factors Might Affect a Woman's Exposure to Estrogen?* examines these different factors in greater detail.

Conclusions

We know that estrogen is essential for normal growth and development of a woman's reproductive system and the breast. Lifetime exposure to estrogen may affect a woman's risk for breast cancer. Understanding how estrogen works in the body and how it may affect the development of breast cancer are critical steps towards making more informed decisions about personal health.

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An extensive bibliography on estrogen and breast cancer risk is available on the BCERF web page (http://www.cfe.cornell.edu/bcerf/).

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The program involves faculty and staff from the Cornell Ithaca campus (College of Agriculture and Life Sciences, College of Arts and Sciences, the College of Human Ecology, the College of Veterinary Medicine, the Division of Biological Sciences and the Division of Nutritional Sciences), Cornell Cooperative Extension, and the Cornell Medical College and Strang Cancer Prevention Center.

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We hope you find this Fact Sheet informative. We welcome your comments. When reproducing this material, credit the Program on Breast Cancer and Environmental Risk Factors in New York State .

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