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BREAST CANCER Prevention INSTITUTE

The **Breast Cancer Prevention Institute** is a research and educational 501(c)(3) public charity with headquarters at
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Phone: 1-86 NO CANCER (1-866-622-6237)
www.bcpinstitute.org

Reproductive Breast Cancer Risks and Breast Lobule Maturation

Who is the single most important person protecting this woman from breast cancer?

BREAST CANCER Prevention INSTITUTE

Her baby!

Long before birth, her baby's chemical signals began the process of breast growth and maturation that make breastfeeding possible. And it is only through a full-term pregnancy and lactation that a woman acquires her greatest protection against breast cancer.

Reproductive breast cancer risks and breast lobule maturation

Breast maturity is closely correlated with known reproductive risk factors for breast cancer. The breast is not fully developed at birth. At full development, the breast is comprised of 15- 25 lobes or segments which are in turn comprised of lobules. Lobules in turn are composed of breast cells.

There are 4 types of lobules whose structural differences appear under the microscope.

These lobules represent different stages of development and maturity of breast tissue.

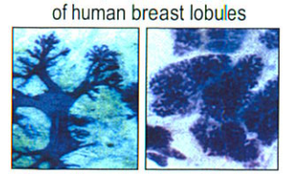
Type 1, 2 & 3 lobules are differentiated by the *average number of ductules per lobular unit*:

Type 1 has *11*; Type 2 has *47*; Type 3 has *80*.

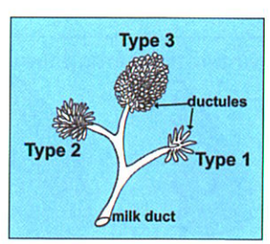
Type 4 lobules are fully matured and contain colostrum or milk.

Type 1 lobules mature into Type 2 lobules under the cyclic influence of the female hormones, estrogen and progesterone, during menstrual cycles. Type 2 lobules only become fully mature into Type 3 then Type 4 lobules under the influence of the hormonal changes of a full-term pregnancy. A major influence in this final stage of maturation into Type 4 lobules is human placental lactogen (hPL) which sharply rises during the last few months of pregnancy. Human chorionic gonadotropin (hCG, which stimulates the ovaries to produce estrogen and progesterone within a few days after conception) and prolactin also play a major role in maturation. HCG and hPL are made in the mother's womb during pregnancy. HCG also stimulates the ovary to produce inhibin, a cancer suppressing hormone, increasing protection of the mother even more.

Actual photomicrographs of human breast lobules

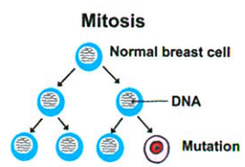


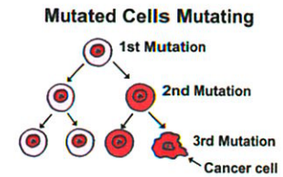
Type 1 Lobule Type 3 Lobule



These 4 types of lobules are also metabolically different and have different breast cancer potential.

Type 1 & 2 lobules have more estrogen and progesterone receptors than Type 3 which cause them to grow through mitosis (cell division) when estrogen and progesterone levels are elevated. Mitosis requires replication of DNA (genes) and therefore can result in mutations.





Mutated cells also undergo mitosis. Multiple mutations can cause cancer cells to form. Cells of Type 1 & 2 lobules also multiply faster than Type 3 resulting in more chances for mutations to occur. This growth (proliferation) under estrogen and progesterone stimulation explains the cancer causing properties of estrogen/progestin combination drugs.

Type 1 lobules are where **ductal cancers** start. These account for at least 85% of all breast cancers.

Type 2 lobules are where **lobular cancers** start. These account for about 12% of all breast cancers.

Type 3 lobules are cancer resistant when they are the result of the regression of **Type 4 lobules** after birth and weaning.

Type 4 lobules are cancer resistant.

The breast maturation process through a normal full-term pregnancy

At birth, after the mother's hormones dissipate, a small amount of breast tissue lies dormant under the infant's nipple & areola.

At puberty, when the ovaries produce cyclic elevations of the female sex steroid hormones, estrogen and progesterone, the breast enlarges. However, only Type 1 and 2 lobules are formed, which are where ductal and lobular cancers start respectively. Most of the breast tissue is stroma (tissue surrounding the lobules). The lobules account for about 10% of the breast tissue.

After puberty, there is a reduction in stroma and lobules account for 30% of the breast tissue: 75% are Type 1 and 25% are Type 2 lobules with a few Type 3.

The "susceptibility window," the period between puberty and a full-term pregnancy, is the time the breast is most susceptible to forming cancer; i.e., when the woman's breast is composed primarily of Type 1 and 2 lobules.

After conception, the baby secretes hCG, stimulating the ovaries to produce the pregnancy hormones estrogen and progesterone, which cause the breast to start to enlarge by making **greater numbers of lobules**. This causes the mother's breast to feel sore and tender.

By the end of the 1st trimester, during the maturation of Type 1 lobules into Type 2, the actual **numbers of these lobules will increase** while the surrounding tissue (stroma) decreases. The breast now has **more places for cancers to start.**

By mid 2nd trimester, the breast has **doubled in volume** and has continued to mature rapidly under the influence of placental lactogen. The breast is now 70% Type 4 cancer resistant lobules and 30% immature cancer susceptible lobules.

By the end of the 3rd trimester, 85% of the breast is fully matured to Type 4 lobules and only 15% remain immature cancer susceptible lobules, leaving **fewer places for cancer to start.**

At delivery, the mother's breasts are now **predominantly Type 4 lobules**. They are fully mature and resistant to carcinogens, resulting in **lower long-term risk of breast cancer for the mother**.

While breastfeeding, the mother's menstrual cycles may stop or become anovulatory, further reducing her risk.

After weaning, Type 4 lobules regress to Type 3 and the breasts get smaller again. However, there is evidence of **permanent changes in the genes** of these Type 3 lobules which confer **life-long cancer resistance** even after menopause when they further regress to Type 1.

These facts of the breast maturation process account for the following known facts about breast cancer risk:

A woman who has a full-term pregnancy decreases her breast cancer risk. A woman who is childless has increased breast cancer risk.

The timing of pregnancy in the course of a woman's reproductive life is crucial to breast cancer risk.

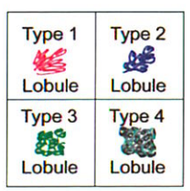
The longer a woman waits before having her first child, the higher her risk because she has a longer "susceptibility window."

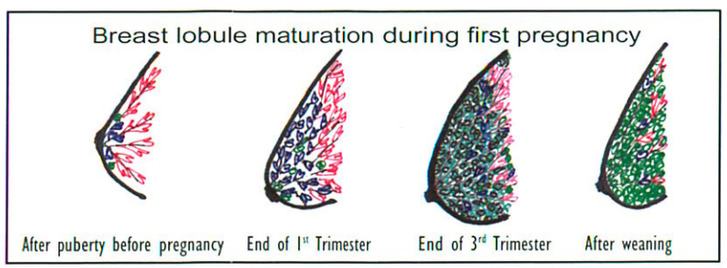
For example, a woman who gives birth at 18 has a 50-75% lower risk of breast cancer than a woman who waits until she is 30.

Each additional birth results in a further 10% risk reduction. Breast feeding reduces risk in proportion to the cumulative length of lactation.

Women who have breast cancer despite prior full-term childbirth, have a higher percentage of Type 1 lobules than women who give birth and do not develop cancer. This is possibly due to a defect in maturation.

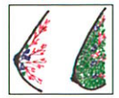
Scientists have been unsuccessful to date in their attempt to create an hormonal "cocktail" to protect childless women from breast cancer.





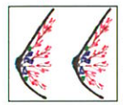
Illustrations of pregnancy outcomes and their effect on breast cancer

***Before and After...*First full-term pregnancy (FFTP):**



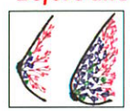
Full-term births cause near complete maturation of the breast to Type 4 lobules therefore **lowering breast cancer risk**. A pregnancy ending between 32 and 36 weeks has about 90% of the protective effect of a full-term pregnancy of 40 weeks. If the first full-term pregnancy occurs late in the woman's reproductive life, her risk is transiently elevated in the first few years post partum. This is due to mutated cells that may have formed during a long "susceptibility window," which then may become cancerous. Cancer cells already present at conception may grow faster under the stimulation of the elevated pregnancy hormones estrogen and progesterone.

***Before and After...*Spontaneous abortion (miscarriage) in the 1st Trimester:**



Approximately 23% of all conceptions end in a spontaneous abortion by 11 weeks in the 1st trimester. This is when the fetus and placenta must make enough hormones to sustain the pregnancy. **In most pregnancies which miscarry during the 1st trimester, pregnancy hormones are lower than in a normal pregnancy, due to either a fetal or ovarian abnormality.** Therefore, the breasts may have never grown more Type 1 & 2 lobules (places where cancers start) in response to the pregnancy or at least very few. This is why women who miscarry will often remark they never "felt" pregnant before the miscarriage. Their breasts were never sore from growing and they were never nauseous from higher than normal hormone levels. **Thus the vast majority of spontaneous abortions (miscarriages) in the 1st trimester do not increase breast cancer risk.**

***Before and After...*Induced abortion in the 1st Trimester:**



Induced abortion of a **normal pregnancy** during which there has been breast growth results in increased risk of breast cancer in the mother. The later in pregnancy an abortion is done, the higher the risk of breast cancer as the more Type 1 and 2 lobules will have formed. **Induced abortion leaves a woman with more places for breast cancer to start.** If an induced abortion is done on a pregnancy which would have spontaneously aborted by 11 weeks, there would be **no** increase in risk. There is some data to suggest that the sooner a woman delivers and nurses a child after having had a prior induced abortion, the smaller the risk increase from the abortion.

Other pregnancy outcomes and breast cancer risk

Premature delivery before 32 weeks:

Premature delivery before 32 weeks is known to more than double breast cancer risk because it leaves the breast with **more places for cancers to start**. The risk is proportional to gestational length. The pregnancy hormone levels are usually normal so the breast changes are those of a normal pregnancy. The effect of premature delivery is the same as in an induced abortion as they differ only in whether the fetus is delivered alive or not. The premature delivery may be caused by multiple gestations (twins, triplets or more with assisted reproduction pregnancies), an incompetent cervix, an induced abortion, or physician-induced labor for fetal abnormalities such as anencephaly.

Spontaneous abortion (miscarriage) in the 2nd Trimester:

The effect would probably be the same as a premature delivery in the second trimester and increase risk. Most 2nd trimester spontaneous abortions occur because of a physical and not hormonal abnormality. For example, there is fetal demise or the mother sustained an injury.

Induced abortion in the 2nd Trimester:

The effect would be the same as a premature delivery before 32 weeks and a spontaneous abortion in the 2nd Trimester. There would be increased risk because there are **more places for cancers to start.** There are data to show there is a 3% increase in breast cancer risk for each week of gestation before the abortion.

Stillbirth:

The death of an infant near or at delivery would not change that full-term pregnancy's protective effect on the breast. There would have been normal maturation of the breast to Type 4 cancer resistant lobules.

Ectopic Pregnancy:

This is the result of an embryo which grows outside of the womb (uterus); e.g. in the mother's Fallopian tube. Its effect on breast cancer risk would most likely be small or minimal as the pregnancy usually ruptures or causes a medical emergency very early on in the pregnancy. There is too little data to be certain of any small risk elevation.