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BCPI FACT SHEET

Breast Development

In the sections to follow, we will address the development of the breast over the lifetime, the development of breast cancer, and the changes that arise in the breast during pregnancy and lactation. We also discuss the occurrence of miscarriage, premature delivery, induced abortion, and full-term pregnancy, and the risk of or protection against breast cancer that these reproductive events provide. As we show, the developmental biology of changes in the breast that occur during puberty and during a normal pregnancy supports the existence of an independent link between induced abortion and breast cancer.

A. Breast Development

Lobule growth

An infant is born with immature alveolar buds and Type 1 lobules under the nipple- areola complex. (A lobule is a unit of breast tissue comprised of a milk duct with surrounding mammary [milk] glands, which are both composed of individual breast cells.) After puberty, females will develop more Type 1 lobules. Some Type 1 lobules will become Type 2 lobules after puberty as the breasts enlarge, at which point the breast contains a mixture of approximately 75 percent Type 1 lobules and 25 percent Type 2 lobules. Type 1 and Type 2 lobules are vulnerable to cancer.

During the first half of pregnancy, the proliferation phase, Type 1 and Type 2 lobules increase in number. By week 20 of a 40-week (full-term) pregnancy, the breast has doubled in volume. The number of lobules in the breast increase through a decrease in the amount of breast stroma, or connective tissue, around the lobules.

During the second half of pregnancy (after week 20), the differentiation phase, these immature, *cancer-vulnerable* Type 1 and Type 2 lobules begin to mature into cancer-resistant Type 4 lobules. Type 4 lobules are capable of producing the milk, or colostrum, the baby will need. After 32 weeks of pregnancy, sufficient Type 4 lobules have developed that a mother is protected against breast cancer, and she begins to incrementally gain the benefit of risk reduction that will maximize at 40 weeks. *By the end of a normal pregnancy,70 to 90 percent of the mother's breast is composed of cancer-resistant Type 4 lobules.*

After birth and after a mother has lactated and breastfed (or should she choose not to breastfeed), Type 4 lobules regress to Type 3 lobules, which retain the epigenetic changes that protect against the development of cancer. This epigenetic change involves the "down-regulation" or "switching off" of lobule reproduction DNA, which thereafter stays permanently switched off and thereby protects against cancer.[23] *A woman's risk of breast cancer will decrease an additional 10 percent with each subsequent pregnancy.*[24] This observed additional reduction in risk may be due to increased breastfeeding among these women, fewer lifetime menstrual cycles, and more anovulatory postpartum cycles (that is, postpartum cycles that do not produce an egg) with lower estrogen exposure, all known to reduce risk. Therefore, the woman who has a full-term pregnancy obtains lifelong benefits from the epigenetic changes it produces in the breast cells and gains even more risk reduction with additional births and breastfeeding.[25]

After menopause, Type 3 lobules morph into what appear to be Type 1 lobules microscopically; however, the epigenetic changes which have afforded cancer resistance remain.

Figure 1: Lobule Development before, during, and after Pregnancy

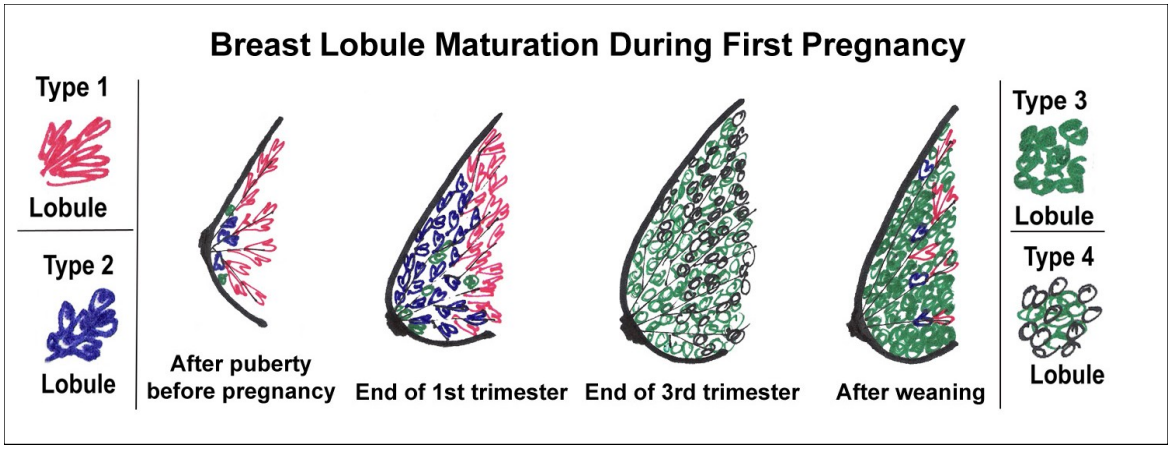


Table 1: Progression of Lifetime Breast Development[26]

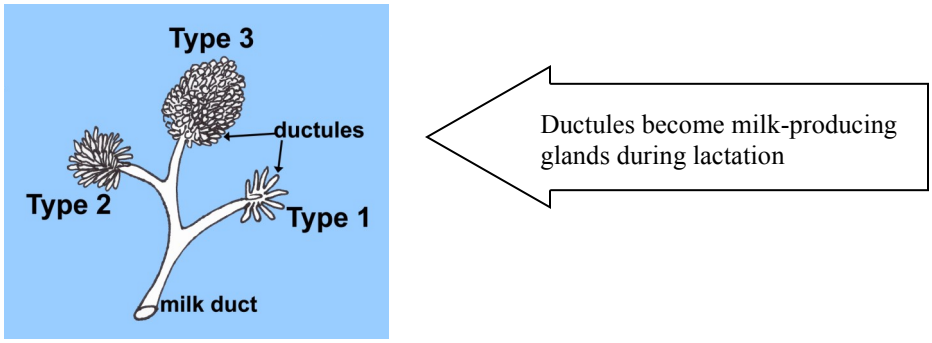
Breast development	State of breast lobule development
After puberty	75 percent Type 1 and 25 percent Type 2 lobules
After conceiving	Increase in Type 1 and Type 2 lobules
At 20 weeks' gestation	Absolute number of Type 1 and Type 2 lobules has greatly increased while stromal[27] breast tissue has decreased as the breast has doubled in volume; maturation into Type 4 lobules commences
At 32 weeks' gestation	Sufficient Type 1 and Type 2 lobules have matured into Type 4 lobules that the mother has a lowered risk of breast cancer
At 40 weeks' gestation	70 to 90 percent of the breasts are cancer-resistant Type 4 lobules
After weaning	Type 4 lobules stop milk production and regress to Type 3 lobules, which have permanent epigenetic changes that protect against cancer
After menopause	Type 3 lobules change morphologically into what appear to be Type 1 lobules; however, their genes do not change in their up- or down-regulation, so risk reduction is maintained

Lobular structure

Again, a lobule is a unit of breast tissue comprised of a milk duct with surrounding mammary (milk) glands, which are both composed of individual breast cells.

The ductules which surround the terminal end, or milk duct, become the glands where milk is produced.[28] Each type of lobule has varying numbers of ductules, which become the milk-producing glands during lactation. These lobules are different morphologically (i.e., in their shape) as well as metabolically (e.g., in their doubling time).

Figure 2: Lobule Types and their Structures



Lobular hormone sensitivity

Type 1 lobules have a greater number of estrogen and progesterone receptors in their cells' nuclei than Type 2 lobules do. Type 2 lobules have significantly more of these receptors than Type 3 lobules. Stimulation of these estrogen and progesterone receptors causes breast cell growth through mitosis (cell division). The more receptors a breast cell has, the more sensitive and reactive it is to hormone levels. Pregnancy (as well as monthly menstrual cycles), which is characterized by elevated estrogen and progesterone levels, causes breast growth.

As stated above, the breast doubles in volume by 20 weeks of pregnancy by reducing the amount of connective tissue (stroma) and increasing the numbers of lobules it contains.[29] By 32 weeks, full differentiation to more cancer-resistant Type 4 lobules, capable of producing colostrum, has occurred in sufficient numbers that the breast is protected against cancer.[30]

All these structural and metabolic changes are regulated by genes turning on and off (epigenetic switches). We know which genes have been "turned off" and "turned on" (down-regulated and up-regulated) throughout a full term of pregnancy[31] under the influence of pregnancy hormones.

Concurrent fetal development

During this time of maternal breast maturation, a parallel development is occurring in the fetus. During the fourth week of pregnancy, the milk streak (area of future breast tissue development) of the embryo forms. Development of the mammary ridge follows in the fifth week, and invasion into the chest wall takes place between the seventh and eighth weeks. (In humans, only two areas of the milk ridge persist in forming breasts.) The solid cords of epithelial cells in the fetal chest wall become canaliculized, or hollow, at 32 weeks, thereby developing the milk ducts and glands of the newly forming fetal breasts.[32]

REFERENCES

[23] A "down-regulated" gene is turned off; an "up-regulated" gene is turned on. A human's cells all contain the same DNA. Turning different genes on or off (epigenetics) produces different kinds of cells. (For example: A liver cell and a skin cell contain the same DNA, but different genes in each cell are up-regulated and down-regulated, which is why some cells are liver cells and others are skin cells.)

[24] Mats Lambe, Chung-cheng Hsieh, Hsiao-wei Chan, Anders Ekbom, Dimitrios Trichopoulos, and Hans-Olov Adami, "Parity, Age at First and Last Birth, and Risk of Breast Cancer: A Population-Based Study in Sweden," *Breast Cancer Research and Treatment* 38 (1996): 305-311.

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[26] J. Russo, Y.-F. Hu, X. Yang, and I. Russo, Chapter 1: "Developmental, Cellular, and Molecular Basis of Human Breast Cancer," Journal of the National Cancer Institute Monographs 27 (2000): 17-37; Jose Russo and Irma H. Russo, "Development of the Human Mammary Gland," in The Mammary Gland, eds. M. Neville and C. Daniel (New York: Plenum Publishing Corporation, 1987).

[27] Stroma is the tissue of the breast that is neither milk ducts nor glands.

[28] The ductules come off the duct draining the lobule called the "terminal end duct." The small terminal ducts drain into larger and larger milk ducts, or lactiferous ducts. These lactiferous ducts transport milk to the lactiferous sinuses, which are just below the nipple.

[29] This is the result of hCG stimulation of estrogen and progesterone production in the first half of pregnancy, which, in turn, stimulates breast cell division.

[30] The mother's hPL levels rise three times higher than her prolactin levels by the end of pregnancy, which enables full differentiation to Type 4 lobules.

[31] Jose Russo, Gabriela A. Balogh, Irma H. Russo, and the Fox Chase Cancer Center Hospital Network Participants, "Full-Term Pregnancy Induces a Specific Genomic Signature in the Human Breast," *Cancer Epidemiology, Biomarkers and Prevention* 17, no. 1 (January 2008): 51-66; I. Verlinden, N. Gungor, K.Wouters, J. Janssens, J. Raus, and L. Michiels, "Parity-Induced Changes in Global Gene Expression in the Human Mammary Gland," *European Journal of Cancer Prevention* 14 (2005): 129-137.

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