Puberty is a key period
Progesterone's role in breast-cancer risk

"We think that puberty may be a time of sensitivity to things that can impact on breast development, and the impact on breast development may have a bearing on future breast cancer risk," said Sandra Haslam, Ph.D., of the Michigan State University Breast Cancer and the Environment Research Center. "The underlying basis of the BCERC is to try to understand how pubertal development is regulated and then, once we have a basic understanding of the underlying mechanisms of development, investigate how environmental stressors affect breast development and may impact breast cancer risk"

With that in mind, she has focused her research on the role of progesterone, which is one of the two major female hormones, in breast development during puberty. The other primary female hormone is estrogen. She said, " Researchers have focused for years and years on estrogen, and people continue talking about estrogen, but if you look at the risk factors for breast cancer, many of them are also associated with exposure to progesterone. These include early onset of menses, late menopause and an early pregnancy." The data on menopausal combined hormone replacement therapy reveal that estrogen plus progestin, rather than estrogen alone, is linked to highest breast-cancer incidence. Dr. Haslam added, "When scientists look at the impact of the estrous cycle on breast tissue in animals and in humans, they consistently find that the greatest amount of proliferation is found during that phase of the cycle when progesterone is present."

She is particularly interested in progesterone's impact at puberty, because the hormone directly stimulates intense growth and expansion of breast epithelial tissue, she explained. Only when scientists understand more about the normal process of breast development and how it is regulated, she asserted, can they begin to understand the effect of diet and other environmental stressors on that development.

Dr. Haslam's lab is contributing the knowledge base for normal breast development by examining two types, or isoforms, of progesterone receptor in mouse and rat mammary glands. These two receptor isoforms, known as progesterone receptors A and B (PRA and PRB), provide the sites for progesterone to dock on the breast cells. Like other hormone-receptor relationships in the body, it is only when progesterone is docked that it becomes active in the cells. The PRA isoform is also remarkable because, according to studies, the receptor may have some function even in the absence of progesterone, she said. " It's very intriguing, because 60 percent of the cells in the pubertal mouse mammary gland have only that isoform of the receptor. The notion that it may be operating by itself tells us that we don't know nearly enough about it or about progesterone."

To study the two isoforms, she and her lab are investigating PRA and PRB in mouse and rat mammary glands. Interestingly, the genes in mice express (produce) only PRA during puberty, while the genes in rats (and in humans as far as we know) nearly always express both PRA and PRB. This PRA-only period in the mice presents a unique opportunity to identify the specific function of that isoform, Dr. Haslam said. "This is important, because PRA is very highly expressed during puberty in mice and rats and we really don't yet know what it's doing. We would never be able to figure it out either in the human or in the rat, because both PRA and PRB are present at almost all times."

Although her research is still under way, her lab has already learned a great deal about breast development, as well as the two receptors' activities, in the mouse model. "In the mouse mammary gland, the major development during puberty is the formation of ducts and that occurs through specialized structures called end buds," she said. The ducts are internal structures that will eventually convey milk to the breast's nipple. By 17-20 weeks, when the mouse mammary gland is fully matured , the mammary gland still has a predominantly ductal organization. With each estrous cycle, some sidebranching of the ducts and development of alveoli occurs, she explained. The alveoli are small round clusters that participate in delivering milk to the ducts. "During pregnancy, we see extensive development of alveoli and the formation of lobules, which become the lactating structures. Finally, after lactation and involution (the post-weaning phase), we have a regression, but it doesn't go back to a pre-pregnancy state," she said.

The receptors also change during breast development. Dr. Haslam's lab found that the mouse expresses PRB only during pregnancy and after involution, but mainly expresses the PRA isoform in the non-pregnant state. She added, "PRA is most highly expressed during puberty in the mouse, whereas PRB is present during lobule formation and appears to mediate that formation." She added, "In mice, only the fully mature gland responds to the exogenous progesterone by producing extensive sidebranches and lobules. This is accompanied by the induction of PRB and a downregulation of PRA."

The rat, which more closely mimics the morphological features of human breast development, has a maturation process and pattern of PR isoform expression that is somewhat different from the mouse, she said, and she is planning to present those results in an upcoming paper.

Ultimately, Dr. Haslam would like to study human tissue to gain a clearer picture of breast development. Through these studies, she hopes to lay the groundwork for future investigations of progesterone's role in breast-cancer risk, especially at puberty when environmental stressors may have a significant impact.

Summary of Dr. Sandra Haslam's presentation at the November 2005 BCERC Scientific Symposium: Normal Mammary Gland Development Characterizing Pubertal – Adult Transition in Mammary Gland Development in the Mouse and Rat Models.