Hormones and breast cancer: controlling the danger within

For the first half of the 20th century, the effects of sex hormones on breast cancer were poorly understood due to the lack of an animal model. In 1959, Charles Huggins devised a method to induce hormone-responsive mammary cancers in rats. The model paved the way for new treatment and prevention strategies for breast cancer.

A hormonal paradox
In 1896, a physician named George Beatson controlled the growth of mammary tumors in women by simply removing their ovaries (1); he thus provided the first connection between breast cancer and the secretions of reproductive organs. But a lack of ovarian function did not guarantee a cancer-free life—breast cancer also occurred in men and older women.

The identification of the ovarian hormone estrogen introduced a new paradox into this still murky area. High doses of estrogen could actually shrink breast tumors in some women. Also, these contrasting treatments—the removal of estrogen sources and the administration of high-dose estrogen—were effective in only one in three women. Further research to resolve these issues was impossible, as mammary cancers in existing mouse models were seldom responsive to hormone treatment.

The perfect model
By the early 1950s, Huggins, who had founded the Ben May Cancer Research Center at the University of Chicago, was already one of the leading experts on the hormonal control of cancer. His discovery that prostate tumors in male dogs could be reduced by castration or by estrogen injection had led to prostate cancer control in a majority of male patients (2).

Huggins next turned to breast cancer and the search for a good disease model. A few years earlier, a researcher had serendipitously discovered that rats of the Wistar strain sometimes developed mammary cancers when fed with a known carcinogen called 3-methylcholanthrene (3-MC) for many months (3).

Huggins predicted that the genetic heterogeneity of outbred rat strains would make them better targets than inbred mouse strains for rapidly and consistently inducing mammary cancers.

He and two postdoctoral researchers began to administer 3-MC in various doses and for different time periods to various strains of female rats. To their surprise, a single high dose was sufficient to induce detectable breast tumors within a month in all 682 of their group of Sprague-Dawley rats. Many of these carcinomas were hormone dependent and decreased in size after an injection of testosterone or removal of either the ovaries or the pituitary.

Huggins published these breakthrough results in *The Journal of Experimental Medicine* in 1959 (4).

This model, which came to be known as the “Huggins tumor,” was the workhorse of breast cancer research for the next two decades. The mechanisms that make 3-MC and other polycyclic compounds potent breast cancer inducers were only recently discovered. Some of their metabolic by-products activate the estrogen receptor (ER), and others alkylate DNA and disrupt gene regulation in mammary cells.

Sorting out differences
Huggins used his model to show that only some cancers were hormone dependent and could be cured by hormone deprivation (5). With Huggins’s encouragement, others at the center later identified ERs and showed that only breast tumors that expressed ERs responded well to surgical removal of the estrogen source (6). When this method failed in some ER–positive patients, Huggins treated their cancers with massive doses of progesterone and estradiol as large doses of these ovarian steroids were known to differentiate breast cells in vitro and decrease their cancer potential (7).

Branching out
Therapeutic treatment was not the only thing on the minds of those using the Huggins model. “We needed to treat not only women with the disease but also women who were at high risk for the disease,” says Craig Jordan, a director of research at the Fox Chase Cancer Center (Philadelphia, PA). In 1973, Jordan traveled to Huggins’s laboratory to learn how the Huggins tumor model could be adapted for prevention purposes. His discovery that the failed contraceptive tamoxifen prevented hormone-driven cancer growth in these rats led to the use of this drug as a chemopreventive agent in pre- and post-menopausal women at high risk (8). Huggins’s discovery of the hormonal dependence of cancer cells in experimental animals thus contributed to solutions for both treatment and prevention. He was awarded the Nobel Prize for Physiology or Medicine in 1966.

REFERENCES