Hormones after breast cancer: Not fuel for the fire after all?

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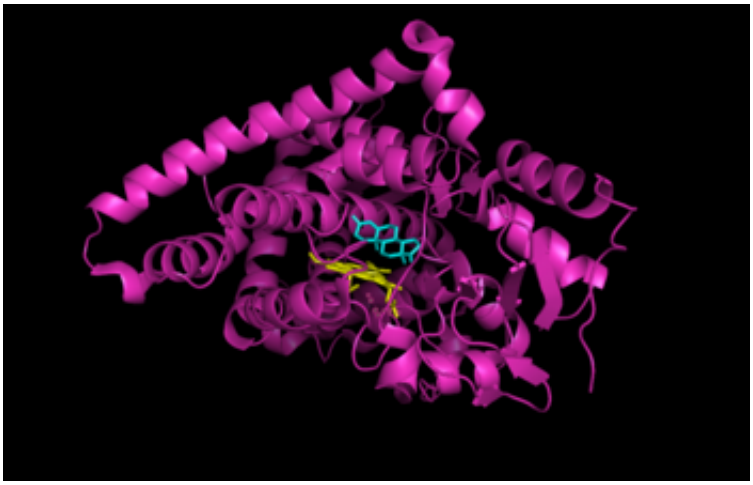

A new study supports a growing body of research suggesting a safe and effective role for natural steroid hormones in treating postmenopausal breast cancer, with fewer detrimental side effects and improved health profile than with standard anti-hormone therapies. The study will be published in final format today in the open-access journal *Reproductive Biology and Endocrinology*.

Breast cancer is the most frequently diagnosed cancer in women in the United States. Approximately 70% of breast cancers are diagnosed in postmenopausal women. Major clinical trials and experimental studies showed that a class of anti-estrogen drugs called aromatase inhibitors

(AIs) is effective against postmenopausal breast cancer. Yet despite their effectiveness in reducing tumor recurrence, aromatase inhibitors have adverse effects on the cardiovascular system and increase osteoporosis and bone fractures, which may explain their lack of overall survival improvement versus the older treatment, tamoxifen. These effects, together with undesirable side effects such as incontinence and bone and joint pain, cause many women to discontinue using AIs. Alternatives are needed.

In their study, researchers at the Center of Excellence in Cancer Research at the Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, set out to explore a radical and counterintuitive hypothesis: Could an optimal choice of hormones lead to improved survival factors and quality of life, enough to outweigh any negative effect on tumor recurrence? Radical—because current standard of practice considers hormone treatment of any type absolutely contraindicated following hormone-receptor-positive breast cancer. Counterintuitive— because estrogen-blocking aromatase inhibitors, a nearly opposite treatment, are the current adjuvant treatment for women after hormone-sensitive breast cancer.

Results from this study in a mouse model suggest the answer to their question is "yes,"—well-chosen hormones could improve both survival and quality of life.

"We are at a very preliminary stage. Our study's results are promising, but we need to know much more. This study provides a good direction," said Rajkumar Lakshmanaswamy, PhD, lead investigator for the study and research director of the Center of Excellence in Cancer Research.

The study was funded by Parsemus Foundation, a nonprofit foundation focused on reproductive health.

Hormones: not all the same

In the experiments, the researchers used the same type of hormones present in the body, because bioidentical hormones have been shown to possess a more positive risk-benefit profile than molecularly altered hormones. In the landmark Women's Health Initiative study, a negative risk-benefit profile was seen with oral equine estrogens plus oral synthetic medroxyprogesterone acetate (PremPro), an older drug combination that continues to dominate the market in English-speaking countries. Estradiol and progesterone delivered non-orally were selected for the experiments in part because of an extensive literature indicating more favorable outcomes.

The results showed that the right combination of hormone treatments reduced the risk of osteoporosis and cardiovascular disease, undesirable health effects associated with estrogen deficiency following menopause. Adding a little testosterone helped even more. Estrogen, progesterone, and testosterone, together (E plus P plus T treatment) was associated with greater physical activity, improved cognition, and better cardiovascular and bone health in the mouse model, and demonstrated the potential significance of hormone treatment in postmenopausal women.

COUNTERINTUITIVE RESULTS

Giving any sort of estrogen after hormone-sensitive breast cancer would generally be considered "throwing fuel on the fire." But the results were counterintuitive: tumor growth was reduced the most by E plus P plus T treatment. Long term, only in one group—the lowest-dose E plus P group—did addition of hormones result in tumor volumes slightly worse than in the control animals, noted Lakshmanaswamy.

"In this study, the aromatase inhibitor did indeed reduce recurrence as expected. However, recurrence rates in the aromatase inhibitor group bounced back up after the 5-year-equivalent treatment period, and the overall improved health outcomes in the hormone groups meant a trend towards greater survival in those groups. Even more notably, two of the regimens were even better than the aromatase inhibitor at preventing tumor growth," said Arunkumar Arumugam, first author of the study.

To date, epidemiological plus animal and laboratory evidence combined suggest that though the recurrence picture is complicated, the majority of women post-breast-cancer will do better on optimized hormones than on anti-hormones, because of better global outcomes, added Elaine Lissner, executive director of the Parsemus Foundation and second author.

"This study indicated that certain hormone regimens, especially adding testosterone, may even result in lower recurrence rates than aromatase inhibitors, on top of better global health outcomes, survival and quality of life. It's another piece of evidence that hormones don't always work the way we assume," said Lissner.

Part of a larger puzzle

V. Craig Jordan, OBE, PhD, DSc, a scientist specializing in medications that treat and prevent breast cancer at the Lombardi Comprehensive Cancer Center, Georgetown University, considers the study an intriguing contribution to a scientific area now receiving a lot of interest. Jordan is widely considered the "father" of tamoxifen, a selective estrogen receptor modulator (SERM) that changed the field of breast cancer treatment. He also proved the anti-cancer effects of raloxifene, another SERM that blocks the effects of estrogen in breast tissue. He now studies how cancer cells can be killed by estrogen after being super-sensitized to it by those very same estrogen-blocking drugs.

The results of this study are consistent with those found in his lab. "This paper has all of the right results for the tumor and the right results for the mouse. It all lines up as far as I'm concerned." The only downside, according to Jordan, is the four-month treatment period for the mice—when women are treated for decades, and tumors are "clever and can change in a heartbeat." "Things happen short term in labs all the time; it's a very hard sell to go from experiments to outside the lab," he said.

The four-month period for mice was designed to be equivalent to five years in a woman's lifespan, and is the same time period used in aromatase inhibitor pre-approval studies. But the trend is towards ever-longer treatment periods with aromatase inhibitors, ten years or more, despite impacts on quality of life.

Next steps

So should women be asking their doctors for hormone treatment rather than anti-hormone treatment after breast cancer? Could the right hormones be more effective at preventing recurrence than aromatase inhibitors, with better quality of life? For the time being, this will remain radical, says Lissner, and only the most open-minded oncologists will be willing to consider the data—despite epidemiological evidence that women who take hormones after breast cancer have much better survival rates than ones who don't.

The next step, according to Lakshmanaswamy, is to determine the hormone dose that is efficient and provides the maximum benefit with the fewest side effects, if any. But with little profit potential and no pharmaceutical company involvement, those studies are unlikely to get done unless the public pushes for taxpayer-funded research. "Our results show that using natural hormones in appropriate combinations suppresses tumor growth and has beneficial effects on cardiac and bone

health, along with better tumor reduction than with current treatments. Many lines of research are coming together now, all pointing in the same direction, but only clinical trials would tell for sure."

More information: *Reproductive Biology and Endocrinology* 2014, 12:66 DOI: 10.1186/1477-7827-12-66

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