Estrogen's Dual Nature? Studies Highlight Effects on Breast Cancer

By Renee Twombly

The story of estrogen's role in breast cancer is starting to look like Dr. Jekyll and Mr. Hyde. A spate of recent studies demonstrates that the hormone—long known to fuel growth of most breast tumors—may actually be effective in treating breast cancer, or even preventing it.

Using estrogen to treat breast cancer is not new—high dose synthetic estrogen DES (diethylstilbestrol) was a mainstay in treatment of metastatic breast cancer in the 1960s and 1970s. But new research has shown that even lower doses of human estrogen (estradiol) has a therapeutic benefit. Furthermore, in the laboratory, scientists are now demonstrating that estrogen can kill breast cancer cells, causing apoptotic death.

Less is known about the effects of estrogen in the prevention setting. However, a recent finding published in *the Journal of the American Medical Association* shows that some menopausal women in the Women's Health Initiative (WHI) who took estrogen had a lower incidence of breast cancer than women on a placebo.

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Still, it is unclear whether these advances will transform estrogen's Mr. Hyde reputation into Dr. Jekyll in the clinic—especially as preventive medicine. While some clinicians never stopped prescribing estrogen to treat breast cancer, others trained in the era of tamoxifen and other anti-estrogenic drugs only know the hormone as a potential carcinogen.

Len Lichtenfeld, M.D., deputy chief medical office at the national office of the American Cancer Society in Washington D.C., is familiar with estrogen's dual nature in treating breast cancer. "In the 1970s, I got responses by putting advanced breast cancer patients on high-dose estrogen, and sometimes, by taking them off of it," he said. "We now think that worked by changing the hormonal environment, and there is not anything wrong with looking at use of estrogen again."

Back to the Future

The first chemotherapy for breast cancer in the 1940s was high-dose estrogen, or DES, which was also used to treat metastatic prostate cancer for more than 40 years, until leuprolide was approved in 1985. Pregnant women also took DES to prevent miscarriages, and for menopausal symptoms.

DES's use in metastatic breast cancer produced a 30 percent response rate and "was considered to be the pioneering application of synthesized chemicals to treat cancer," said V. Craig Jordan, Ph.D., D.Sc., of Georgetown Lombardi Cancer Center.

"Large tumors would just melt away, but you needed sledgehammer doses to do it—50 times more than a woman would normally have in her body," said Jordan, who is credited with developing tamoxifen in 1974, and later, with proving the anti-cancer effects of raloxifene, another selective estrogen receptor modulator that blocks the effects of estrogen in breast tissue.

But when the Mayo Clinic's 1981 head-to-head comparison of tamoxifen with DES showed similar response rates—and far fewer adverse responses in tamoxifen users—breast oncologists switched *en masse* to the newer agent. By that time, DES had also gained a reputation for producing a rare vaginal tumor cancer in so-called "DES daughters" of women who used DES to sustain their pregnancy.

Estrogen's Comeback

Interest in DES was rekindled following a 1999 long-term follow-up of the original Mayo Clinic study showed patients treated with DES had increased survival compared to tamoxifen-treated patients.

Then, in 2001, a Norwegian study of 32 breast cancer patients who had become resistant to endocrine therapy showed almost half of the participants responded to high-dose DES.

Two years ago, Matthew Ellis, M.D., Ph.D., director of the breast cancer program at Washington University in St. Louis, published a key study in *JAMA* on the treatment of breast cancer using oral estradiol, identical to the principal active form of estrogen in a women's body. Ellis found that low-dosage estradiol (6 milligrams), a level similar to that found in premenopausal women, was as effective as 30-milligram dosages, the amount found in pregnant women. Tumors shrank or stopped growing in about 30% of women in both investigational groups, but toxicity was reduced in the low-dose group.

V. Craig Jordan, Ph.D., D.Sc.

Some of the cancers recurred, but about a third of those women then responded again to the anti-estrogenic aromatase inhibitors. That meant that patients who had previously taken aromatase inhibitors but had become resistant to them experienced tumor shrinkage using estradiol—a treatment that costs $1 a day. Later, after they became resistant to estrogen, they responded to anti-estrogens again, said Ellis. These treatments were much better tolerated than chemotherapy would have been, Ellis said, adding, "This strategy is very effective in a select group of patients."

Jordan has focused his Georgetown lab on understanding how estrogen kills breast cancer cells that have become resistant to

the anti-estrogenic effects of tamoxifen, raloxifene, and aromatase inhibitors.

"After five years of anti-estrogen therapy, a switch takes place inside breast cancer cells and resistance to these agents develops," he said. "Now when you use estrogen, it triggers [cancer cell] death and not growth." Jordan adds that if researchers can find the mechanism that pulls this trigger, it may be possible to come up with a new, targeted therapy that mimics estrogen in its Dr. Jekyll guise.

Estrogen's Role in Prevention

According to some researchers, the estrogen-only part of the WHI study, involving 10,739 women with hysterectomies, proves the value of estrogen as an anti-cancer agent.

A recent analysis, presented at the San Antonio Breast Cancer Symposium in December, detected a statistically significant effect in subgroup analyses, which included most of the participants enrolled in the trial: a 32% breast cancer relative reduction in the 8,500 women without a family history of the disease (80% of study participants), and 43% in the 7,600 women with no history of benign disease (71% of study participants), compared to participants who used a placebo.

That study, by University of British Columbia researcher Joseph Ragaz, M.D. and colleagues, followed a previous *Cancer Research* report in 2009 on estrogen's protective effects against breast cancer.

These findings are strong enough to suggest that use of estrogen as a chemopreventive "is plausible and needs urgent verification," Ragaz said.

An article in the April 6 issue of *JAMA*, found a smaller, but statistically significant protective effect in WHI participants who took estrogen alone. After 10.7 years of follow-up (including about 6 years of treatment), women randomized to estrogen treatment had a 23% lower relative risk for breast cancer compared to women who used a placebo—151 breast cancers were seen in the treatment group (out of 5,310 total women) versus 199 in the placebo group (out of 5,429 women). The effect held across postmenopausal women aged 50-80. "We weren't expecting this persistent reduced risk of breast cancer," said the study's lead author, Andrea LaCroix, Ph.D., an epidemiologist at the Fred Hutchinson Cancer Research Center in Seattle.

"It could be the first randomized trial evidence that if you give healthy women estrogen, without progestin, it actually appears to reduce breast cancer," she said. "And if you look carefully back at the observational studies of hormone replacement, they have odds ratios and hazard ratios of less than 1 for estrogen alone. It's never been interpreted as possible prevention, because we just didn't have that frame of mind."

But laboratory and clinical research is starting to counter that view. According to Jordan and Leslie Ford, M.D., associate director for clinic research in the National Cancer Institute's Division of Cancer Prevention, "nascent" breast cancer cells may have an apoptotic response to exogenous estrogen after the estrogen deprivation caused by menopause.

In a commentary published in the online April 10 edition of *Cancer Prevention Research*, they say the WHI findings "provide additional evidence that the strategy to decipher the mechanism of physiologic estrogen to induce apoptosis has significance for both treatment and prevention."

Estrogen's Future

Some researchers are endorsing estrogen's paradigm shift more than others.

While Ragaz thinks the hormone should be used for breast cancer prevention, LaCroix argues that the WHI findings need further parsing—especially given estrogen's effect on conditions other than breast cancer. In women aged 50–60, estrogen offered substantial protection against coronary heart disease, colorectal cancer and all-cause mortality.

This is good news for postmenopausal women in their 50s, one-third of whom have had a hysterectomy, LaCroix said. "It's important to realize that all these health effects were produced among women who were mostly followed longer off of hormone therapy than on it. It's a lot of stuff to be happening with a single pill."

But some researchers say the timing of estrogen use is crucial given that some studies, such as the Million Women Study in the United Kingdom and the estrogen-progestin arm of the WHI, found that use of hormones within 5 years of menopause was associated with elevated breast cancer risk compared to later use.

According to Emily Jungheim, M.D., who co-authored the editorial on the recent *JAMA* article, since 68% of women who participated in WHI were older than 60 when they enrolled, the new WHI estrogen-only analysis cannot address the issue of using estrogen before or during menopause. "An important question that emerges is whether the WHI population is appropriate for reaching definitive conclusions regarding younger women and the risk of breast cancer association with hormone therapy," said Jungheim, who is an assistant professor of obstetrics and gynecology at Washington University School of Medicine in St. Louis.

Still others stand behind anti-estrogenic drugs, arguing that women at risk for breast cancer can derive twice as much preventive benefit from tamoxifen and raloxifene.

JoAnn Manson, M.D., Dr.P.H., one of the principle investigators of WHI, says that it may be possible that the preventive effects seen in the study might be due to the notion that the estrogen compound used acts like tamoxifen.

"One of the theories is that conjugated estrogen may be a weaker form of estrogen that is blocking the receptors from a woman's natural estrogen, analogous to tamoxifen," said Manson, a professor in the department of epidemiology at the Harvard School of Public Health.

"A piece of evidence supporting this idea is that the protective effect seen in the WHI estrogen-only arm lasted for years after stopping, which is also the case with tamoxifen," she said. If that's true, she added, more natural estrogenic replacement such as estradiol and bioidentical estrogen in use today may not offer such a protective effect.

In the meantime, the findings of the WHI estrogen-only study, according to Manson, "provide reassurance for women who use estrogen therapy for management of menopausal symptoms that there is a favorable benefit-risk profile for many other outcomes."

Dr. LaCroix has reported serving on scientific advisory committees for research studies for Warner Chilcott and Sanofi-aventis, Amgen, and Pfizer. Dr. Ragaz has reported serving on advisory boards for GlaxoSmithKline, Novartis, Roche, and Sanofi-aventis.

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