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Estrogen Alone is Effective for Reducing Breast Cancer Risk

- Exogenous estrogen (administered as HRT) reduces breast cancer rates.
- HRT based on estrogen alone helps manage menopausal symptoms.
- More data are needed to elaborate on estrogen's role in chemoprevention.

SAN ANTONIO — While endogenous estrogen (i.e., estrogen produced by ovaries and by other tissues) does have a well-known carcinogenic impact, hormone replacement therapy (HRT) utilizing estrogen alone (the exogenous estrogen) provides a protective effect in reducing breast cancer risk, according to study results presented at the 33rd Annual CTRC-AACR San Antonio Breast Cancer Symposium, held Dec. 8-12.

"Our analysis suggests that, contrary to previous thinking, there is substantial value in bringing HRT with estrogen alone to the guidelines. The data show that for selected women it is not only safe, but potentially beneficial for breast cancer, as well as for many other aspects of women's health," said lead researcher Joseph Ragaz, M.D., medical oncologist and clinical professor in the faculty of medicine, School of Population and Public Health at The University of British Columbia, Vancouver, BC, Canada.

"These findings should intensify new research into its role as a protective agent against breast cancer," he added.

Ragaz and colleagues reviewed and reanalyzed data from the Women's Health Initiative (WHI) hormone replacement therapy trials. WHI is a national health study that focuses on strategies for preventing heart disease, breast and colorectal cancer, and fracture in postmenopausal women. The WHI was launched in 1991 and includes more than 161,000 U.S. women aged 50 to 79 years.

"Over the last 30 years HRT has been used almost indiscriminately by women expecting the benefit of reducing cardiac risks, while providing a protective effect against bone

-more-

fracture, and improving overall quality of life," said Ragaz. "The WHI results as originally interpreted led to a major pendulum swing against HRT."

The WHI HRT trial consisted of two cohorts of women; the estrogen-alone group of women without a uterus and the estrogen-plus-progestin group of women with a uterus.

Ragaz and colleagues reanalyzed the WHI studies in more detail and found that subsets of women with no strong family history of breast cancer who received estrogen alone had a significantly reduced breast cancer incidence. In addition, the 75 percent of women without benign disease prior to the trial enrollment also had a reduced breast cancer risk.

"Reduction of rates of breast cancer in the majority of women who are candidates for estrogen-based HRT is a new finding because estrogen was always linked with a higher incidence of breast cancer," Ragaz said, "yet estrogen administered exogenously is actually protective for most women."

Based on the results of this current analysis, Ragaz suggested that "while the use of HRT with estrogen alone may reduce the risk of breast cancer and may also be appropriate to manage menopausal symptoms, further research is warranted to elaborate on the optimum treatment regimen, to refine the selection of ideal candidates for estrogen therapy, and to understand the estrogen mechanisms that support the prevention of human breast cancer."

"The recommendations based on prior analyses of the results of the WHI HRT studies was not to use HRT, but we are optimistic this will change," he said. "Our conclusion, based on the data presented, should enhance considerations for an early approval of HRT based on estrogen-alone for the majority of selected women suffering with menopausal symptoms and galvanize new research on HRT to define the optimum regimens for individual women."

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The mission of the CTRC-AACR San Antonio Breast Cancer Symposium is to produce a unique and comprehensive scientific meeting that encompasses the full spectrum of breast cancer research, facilitating the rapid translation of new knowledge into better care for breast cancer patients. The Cancer Therapy & Research Center (CTRC) at The University of Texas Health Science Center at San Antonio, the American Association for Cancer Research (AACR) and Baylor College of Medicine are joint sponsors of the San Antonio Breast Cancer Symposium. This collaboration utilizes the clinical strengths of the CTRC and Baylor, and the AACR's scientific prestige in basic, translational and clinical cancer research to expedite the delivery of the latest scientific advances to the clinic. The 33rd annual symposium is expected to draw nearly 9,000 participants from more than 90 countries.

Presenter: Joseph Ragaz, M.D., FRCP

Abstract Number: 1410

Title: Dual Estrogen Effects on Breast Cancer: Endogenous Estrogen Stimulates, Exogenous Estrogen Protects. Further Investigation of Estrogen Chemoprevention Is Warranted.

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Abstract Body:

Until the randomized Women Healths Initiative [WHI] trials 1,2, most hormone replacement therapy (HRT) studies showed an association of HRT with higher BrCa risk. However, our recent reviews of the WHI trials suggested that Estrogen alone can be protective while HRT based on Estrogen + Progestin can be carcinogenic 3, 4.
In this analysis, we expand this concept to examine the difference between "Exogenous" Estrogen - delivered as part of HRT, versus "Endogenous" Estrogen - i.e. E produced by human tissues.
Rationale 1: Endogenous E is carcinogenic.
Reducing E levels through oophorectomy, selective oestrogen receptor modulators (SERMs) or with aromatase inhibition is effective at all stages of oestrogen receptor positive breast cancer and is significantly protective against BrCa in high risk women 5.
Rationale 2: Exogenous E Protective:
Updates of the WHI trial 2 [women with hysterectomy, randomized to E alone versus Placebo, 1,2] with analyses according to prior history of Benign Breast Disease (PH BrD); a first degree relative with BrCa (PH 1st Rel BrCa); or prior HRT use, show:

Results of the WHI trial 2

WHI Trial 2	N%	HR	95% C.I.
All participants	10,739 (100%)	0.80	0.62 - 1.04
No PHBrD	7,681 (71.5%)	0.57	0.51 - 0.78*
NO PH1st Rel BrCa	8,554 (80%)	0.68	0.50 - 0.92*
No prior History of HRT	5,763 (53.7%)	0.65	0.46 - 0.92*

* $p < 0.05$

Conclusion: These data are compatible with a dual estrogen effect where Exogenous Estrogen is protective, in contrast to the carcinogenic impact of Endogenous Estrogen. The protective effect of Estrogen is comparable in magnitude to that reported with tamoxifen in high risk women. Based on these data, we propose that:

1. In selected women - [i.e. the majority of the WHI HRT trial 2 participants, 71.5 - 80%] - the use of HRT based on Estrogens alone may be appropriate to manage menopausal symptoms, as it is associated with a significant reduction of BrCa rates.
2. The use of Exogenous Estrogen in chemoprevention merits validation, with the optimum Estrogen regimen determination [type of Estrogens; dose; mode of delivery, etc.] high priority.

References:

1. WHI working Group Reports, JAMA 2002; 2004; 2006
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3. Cancer Res 2009; 69; # 908
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5. Diseases of Breast, the 3rd Edition, 2005