Embargoed for Release: 7:30 a.m. CT, Dec. 13, 2019

To interview Rowan Chlebowski, contact Julia Gunther at julia.gunther@aacr.org or 215-446-6896. For a photo of Chlebowski, click here.

Long-term Follow-up Shows Estrogen Alone and Estrogen Plus Progestin Have Opposite Effects on Breast Cancer Incidence in Postmenopausal Women

Estrogen alone decreased, while adding progestin increased, breast cancer incidence

SAN ANTONIO — Long-term follow-up results from two large, randomized, placebo-controlled Women's Health Initiative (WHI) trials in postmenopausal women showed that the use of estrogen alone as menopausal hormone therapy decreased breast cancer incidence and death with persistent results after discontinuation of use, while estrogen plus progestin increased breast cancer incidence with persistent results after discontinuation of use, according to results presented at the San Antonio Breast Cancer Symposium, held Dec. 10-14.

"Menopausal hormone therapy with estrogen plus progestin (for postmenopausal women with an intact uterus) and estrogen alone (for postmenopausal women with prior hysterectomy) continues to be used by millions of women worldwide," said Rowan T. Chlebowski, MD, PhD, chief of the Division of Medical Oncology and Hematology at Harbor-UCLA Medical Center, and an investigator at The Lundquist Institute. "Nonetheless, after nearly half a century, menopausal hormone therapy influence on breast cancer incidence and mortality remains unsettled, with discordant findings from prospective observational studies compared to findings from randomized clinical trials."

Earlier this year, findings published by the Collaborative Group on Hormonal Factors in Breast Cancer from a meta-analysis of 58 observational studies showed estrogen plus progestin as well as estrogen alone were both associated with significantly increased risk of breast cancer incidence, while in the Million Women Study, both estrogen plus progestin as well as estrogen alone were associated with significantly increased breast cancer mortality.

The current report updates earlier findings from two randomized WHI clinical trials on breast cancer incidence and breast cancer mortality in women randomly assigned to conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA), CEE alone, or placebo, with more than 19 years of cumulative follow-up.

"In the two randomized, placebo-controlled WHI clinical trials involving 27,347 postmenopausal women, CEE plus MPA significantly increased breast cancer incidence, with these adverse effects persisting over a decade after discontinuing use," noted Chlebowski. "And in contrast to decades of observational study findings, in the WHI trial, CEE alone significantly reduced breast cancer incidence and significantly reduced deaths from breast cancer, with these favorable effects persisting over a decade after discontinuing use."

Chlebowski added, "While there are differences in characteristics of participants in the observational studies compared with those in the WHI randomized trials, the discordance

between the randomized clinical trial findings with respect to estrogen alone use and observational findings are difficult to reconcile."

Chlebowski and colleagues enrolled postmenopausal women aged 50 to 79 years with no prior breast cancer in one of two randomized clinical trials at 40 U.S. centers from 1993 to 1998, and followed the patients through September 2016. Postmenopausal women with an intact uterus received CEE and MPA (8,506) or placebo (8,102) for a median of 5.6 years. Postmenopausal women who had undergone hysterectomy received CEE alone (5,310) or placebo (5,429) for a median of 7.2 years.

After 16.1 years of cumulative follow-up, among those who received CEE alone, there were 520 incident breast cancers during the post-intervention period. Compared with women who had received placebo, those who had received CEE were 23 percent less likely to have been diagnosed with breast cancer and 44 percent less like to die from the disease, and these positive outcomes are in agreement with the earlier findings from this trial during the intervention period.

After 18.3 years of cumulative follow-up, among those who received CEE plus MPA, there were 1,003 incident breast cancers during the post-intervention period. Compared with women who had received placebo, those who had received CEE plus MPA were 29 percent more likely to have been diagnosed with breast cancer, and this negative outcome is in agreement with the earlier finding from this trial during the intervention period. CEE plus MPA was associated with an increased risk for death from breast cancer in the extended analysis, but it did not reach statistical significance.

Key limitations of the study include that the breast cancer mortality analyses were not protocol-specified. However, death from breast cancer is the most clinically relevant breast cancer outcome, Chlebowski noted. In addition, the trials evaluated one dose and schedule of CEE plus MPA or CEE alone, respectively, and findings may not apply to other preparations, doses, or schedules.

The WHI program is supported by the National Heart, Lung, and Blood Institute; National Institutes of Health; Department of Health and Human Services; and the National Cancer Institute. Chlebowski has received honoraria from Novartis, AstraZeneca, and Genentech; and consulting fees from Novartis, AstraZeneca, Pfizer, Puma, Immunomedics, and Genentech.

ABSTRACT

Publication Number: GS5-00

Long-term influence of estrogen plus progestin and estrogen alone use on breast cancer incidence: The Women's Health Initiative randomized trials

Rowan T Chlebowski[1], Garnet L Anderson[2], Aaron K Aragaki[2], JoAnn E Manson[3], Marcia Stefanick[4], Kathy Pan[1], Wendy Barrington[5], Lewis H Kuller[6], Michael S. Simon[7], Dorothy Lane[8], Karen C Johnson[9], Thomas E. Rohan[10], Margery L.S. Gass[2], Jane A Cauley[6], Electra D. Paskett[11], Maryam Sattari[12] and Ross L Prentice[2]. [1]Los Angeles BioMedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA;[2]Fred Hutchinson Cancer Research Center, Seattle, WA;[3]Brigham and Women's Hospital, Boston, MA;[4]Stanford Prevention Research Center, Stanford, CA;[5]University of Washington, Seattle, WA;[6]Pitt Public Health, Pittsburgh, PA;[7]Karmanos Cancer Institute, Detroit, MI;[8]Stony Brook University, Stony

Brook, NY;9University of Tennessee Health Science Center, Memphis, TN;10Albert Einstein Cancer Center, Bronx, NY;11The Ohio State University, Columbus, OH;12UF Health Internal Medicine, Gainesville, FL

Background: Breast cancer outcomes from the Women's Health Initiative (WHI) Estrogen plus Progestin and Estrogen alone trials have been reported but issues remain regarding long- term, post-intervention influence on breast cancer incidence and the influence of time from menopause to hormone therapy initiation (gap time) on breast cancer findings.
Design and methods: Postmenopausal women aged 50 to 79 years with no prior breast cancer and with mammogram clearance enrolled in one of two randomized clinical trials at 40 US centers from 1993 to1998, with follow up through September, 2016. The randomized, placebo-controlled trial interventions were: conjugated equine estrogens (CEE, 0.625 mg/d) plus medroxyprogesterone acetate (MPA, 2.5 mg/d) (n = 8,506) vs placebo (n = 8,102) for 5.6 years (median) for women with a uterus or CEE-alone (n = 5,310) vs placebo (n = 5,429) for 7.2 years (median) for women with prior hysterectomy. Annual mammography was mandated through the originally specified completion date in both trials (March 31, 2005). Incident breast cancers were verified by medical record review. Hazard ratios (HRs) were estimated using multivariable Cox proportional hazards models. The primary outcome for these analyses was time-specific invasive breast cancer incidence rates. In each trial, participants were instructed to stop all study pills coincident with the publication of each trial's results, in 2002 and 2004, respectively.
Results: During the intervention period, with 238 incident breast cancers, CEE-alone significantly reduced breast cancer incidence (hazard ratio [HR] 0.76 95% confidence interval [CI] 0.58, 0.98, P = 0.04). As previously reported, subgroup analyses indicated CEE-alone was particularly beneficial for women with no prior HT use (interaction P = 0.04) and women with gap time >= 5 years (interaction P = 0.01). Post-intervention, through 16.1 years of cumulative follow-up, with 520 incident breast cancers, CEE-alone use continued to significantly reduce breast cancer incidence (HR 0.77 95% CI 0.65-0.92, P = 0.005) while subgroup differences were attenuated and were no longer statistically significant. During the intervention period, with 360 incident breast cancers, CEE plus MPA use significantly increased breast cancer incidence (HR 1.26 95% CI 1.02, 1.56, P = 0.04) with increase in breast cancer incidence greater in women with prior HT use (interaction P = 0.02) and women with gap time < 5 years (interaction P = 0.002). Post-intervention, through 18.3 years cumulative follow-up, with 1,003 incident breast cancers, CEE plus MPA continued to significantly increase breast cancer incidence (HR 1.29 95% CI 1.14, 1.47, P < 0.001) while subgroup differences were attenuated and were no longer statistically significant.
Conclusions: CEE-alone and CEE plus MPA use have opposite effects on breast cancer incidence. CEE alone significantly decreases breast cancer incidence which is long term and persists over a decade after discontinuing use. CEE plus MPA use significantly increases breast cancer incidence which is long term and persists over a decade after discontinuing use. As a result of the attenuation of subgroup interactions: all postmenopausal women with prior hysterectomy using CEE-alone have the potential benefit of experiencing a reduction in breast cancer incidence while all postmenopausal women using CEE plus MPA have the potential risk of experiencing an increase in breast cancer incidence.

# # #

Follow the meeting on Twitter: @SABCSSanAntonio and #SABCS19

About SABCS®
Since 1977 the San Antonio Breast Cancer Symposium® (SABCS®) has been the leading scientific conference for basic scientists, physician-scientists, clinical investigators and breast care providers, and advocates seeking an exchange of new information in experimental biology, etiology, prevention, diagnosis, and therapy of premalignant breast disease and breast cancer. Founded, owned, and operated by UT Health San Antonio, the symposium has grown to a five-day event attended by an international audience of academic investigators and private physicians from over 80 countries to attain information through abstract presentations, panel discussions, research findings, and state-of-the-art educational sessions. UT Health San Antonio, the American Association for Cancer Research (AACR), and Dan L Duncan Comprehensive Cancer Center at Baylor College of Medicine support SABCS, which provides education and accessibility to the latest information regarding the prevention, diagnosis, and treatment of premalignant breast cancer and breast disease. For more information about the symposium, please visit www.sabcs.org.