**BY BRUCE JANCIN**  
*FROM THE SAN ANTONIO BREAST CANCER SYMPOSIUM*

**Dual-Hormone Therapy May Boost Ca Mortality**

**VITALS**

**Major Finding:** After 11 years of follow-up, the incidence of breast cancer is up by 25% in the dual-hormone therapy group relative to placebo. Yet the relative increase in mortality is 96%.  
**Data Source:** An updated analysis of the Women’s Health Initiative randomized trials.  
**Disclosures:** Dr. Chlebowski disclosed that he receives grant support from Amgen and is on the speakers bureaus for AstraZeneca and Novartis. Dr. Coates reported having no relevant financial disclosures.

SAN ANTONIO – Menopausal hormone therapy with estrogen plus progesterin doubles a woman’s risk of death from breast cancer, nearly doubles the risk of death from non-small cell lung cancer, and increases the risk of death from colorectal cancer by 54%, according to an updated analysis of the Women’s Health Initiative randomized trials.

Because breast and lung cancer are the top-two causes of cancer mortality in women, these are sobering findings with important clinical implications, Dr. Rowan T. Chlebowski observed at the symposium.  

“The 54% increased risk of death after diagnosis of colorectal cancer in Women’s Health Initiative (WHI) participants who were randomized to combined-hormone therapy rather than placebo was a trend that did not achieve statistical significance. But it is nonetheless a finding that crushes the enthusiasm that greeted an earlier WHI report of a 44% reduction in the incidence of colorectal cancer in combined-hormone therapy users after 5.6 years of follow-up (N. Engl. J. Med. 2004;350:991-1004).”

“One cannot take forward the 44% relative risk reduction in colorectal cancers as being a positive finding,” said Dr. Chlebowski, professor of medicine at the University of California, Los Angeles.

Given the initial observation of fewer colorectal cancers being diagnosed in the combined-therapy arm of the WHI, investigators were quite surprised by the tumor characteristics of these cancers at time of diagnosis. The colorectal cancers arising in the combined-therapy group—although fewer in number—were much higher risk.

In all, 76% of them were pathologically staged as regional or metastatic disease, compared with 48% of colorectal cancers in women on placebo, and 39% percent of the colorectal cancers detected in combined-hormone therapy users were lymph node positive, compared with just 29% in placebo-treated controls.

The WHI consisted of two separate National Institutes of Health-funded, randomized trials that profoundly altered the management of menopausal symptoms. In the early 1990s, more than 15% of U.S. women are current smokers, Dr. Chlebowski noted.

Turning to the results of the estrogen-alone WHI trial, he pointed out that the therapy had no impact on incidence or death rates from lung or colorectal cancer, relative to placebo, but there was a nonsignificant 20% reduction in the relative risk of breast cancer in the hormone therapy group. This trend for a breast cancer-reduction benefit achieved significance in the nearly 4,500 study participants who were randomized to estrogen alone or placebo 5 years or more following the last menstrual period, where the hormonal therapy group enjoyed a 37% relative risk reduction. Of course, that’s not how hormone therapy is ordinarily employed in clinical practice, the physician pointed out.

One audience member rose to say that she thought the oft-quoted sharply increased risk of estrogen and progestin [combination] is doing something to the behavior of existing tumors, compared with controls. Also noteworthy were the combined-therapy group’s adjusted 78% increase in triple-negative cancers, the twofold increase in HER2-overexpressing tumors, and the 37% increase in HER2-negative tumors.

Nearly all the increase in lung cancer deaths associated with dual-hormone therapy resulted from NSCLC. Hormone therapy had no effect upon small cell lung cancer rates.

Among current smokers, the cumulative risk of death from lung cancer was 3.42% in those who used dual-hormone therapy for 5-plus years and 2.39% in placebo-treated controls. In other words, in 100 current smokers who used estrogen plus progesterin for 5-plus years experienced an otherwise-avoidable death from NSCLC.

Among past smokers, the rate was 1 in 200. These numbers are worth keeping in mind, given that today roughly 15% of U.S. women are current smokers, and 35% are past smokers, Dr. Chlebowski noted.

Sources: Medco 2010 Drug Trend Report; R&D Directions 2009;15:4-89

“Dr. Chlebowski said he thinks it’s certainly an appropriate research project, but he’d advise against trying it in clinical practice, given the product labeling and the malpractice lawsuit climate.”

His take-home message from the expanded WHI analysis: “Even short-term use of combined-hormone therapy should be reserved for women with limiting climacteric symptoms [that are] not manageable by other means.”

In a conference-closing review of the past year’s top developments in early breast cancer, Dr. Alan Coates singled out Dr. Chlebowski’s presentation on the WHI results as hands-down the most important study of the year in the field of cancer epidemiology.

“As we’ve known before, there’s a small but real increase in the incidence of breast cancer with combined-hormone replacement. The new finding is that there’s a massive increase—a doubling—in mortality from breast cancer.”

“And the mortality increase isn’t confined to breast cancer. … This disparate increase in mortality over incidence in several tumor types suggests that the estrogen and progestin [combination] is doing something to the behavior of existing tumors,” commented Dr. Coates of the University of Sydney.

It may be, as Dr. Chlebowski proposed, that the mechanism involves the angiogenic pathway, but other investigators have demonstrated that under certain circumstances, progesterogens can stimulate stem cells by a paracrine RANKL (receptor-activated nuclear factor-κB ligand) mechanism. This could provide an equally plausible alternative explanation, Dr. Coates said.

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**DATA WATCH**

**Cancer Drugs Fill Pharmaceutical Pipeline**

Cancer  | 831  
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CNS  | 329  
Infections  | 229  
Pain/inflammation  | 204  
Cardiovascular  | 191  
Diabetes/metabolism  | 166  
Respiratory disorders  | 137  
Gastrointestinal  | 87  
Blood disorders  | 83  
Dermatologic  | 66  

Note: Includes drugs in phase I, phase II, and phase III or awaiting FDA approval for the top 10 areas of development in 2009.

Sources: Medco 2010 Drug Trend Report; R&D Directions 2009;15:4-89