WHI: New Findings on Big-Three Cancer Rates

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FROM THE SAN ANTONIO BREAST CANCER SYMPOSIUM

SAN ANTONIO – Menopausal hormone therapy with estrogen plus progestin 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, observed Dr. Rowan T. Chlebowski, professor of medicine at the University of California, Los Angeles.

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 didn't achieve statistical significance. But it's 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).

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 59% 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 40% of all postmenopausal women were on hormonal therapy with estrogen alone or in combination with progestin. Following the initial WHI report of multiple adverse effects of estrogen plus progestin, the popularity of hormone therapy dropped off the table.

One WHI study involved 16,608 postmenopausal women aged 50-79 years with an intact uterus who were randomized to estrogen plus progestin or to placebo for a median of 5.6 years. The other study included 10,739 postmenopausal women with prior hysterectomy who were randomized to conjugated equine estrogens alone or placebo for an average of 7.1 years.

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DR. CHLEBOWSKI

In the examination of WHI trends for the big-three (breast, lung, and colorectal) cancers in women, there is a consistent disparity between their relatively modestly increased incidence in dual-hormone therapy users, relative to placebo, and the far larger death rates resulting from these cancers. For example, 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%. Similarly, the incidence of non–small cell lung cancer (NSCLC) was 23% greater in women on combined-hormone therapy than in those on placebo, but the risk of death from NSCLC was 87% greater.

"The greater effect of estrogen and progestin on deaths from breast, lung, and colorectal cancer – [compared with] the effect on incidence – [suggests that] combined-hormone therapy facilitates growth and metastatic spread of established cancers, perhaps mediated by angiogenesis stimulation," the oncologist said, adding that "in a variety of preclinical models, estrogen and progestin are potent angiogenesis stimulators."

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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.

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The investigators' initial hypothesis was that nearly all the increase in breast cancers associated with combined-hormone therapy would involve estrogen receptor–positive tumors. Not so. In fact, the new analysis – based upon 11 years of follow-up and 678 cases of breast cancer – shows that all breast cancer subtypes appear to be increased, relative to rates in the placebo arm.

For example, combined-hormone therapy was indeed associated with an adjusted 27% greater increase in estrogen receptor–positive breast cancers than with placebo in a multivariate analysis, but it was also associated with a 40% increase in estrogen receptor–negative 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, 1 in 100 current smokers who used estrogen plus progestin 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, he 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 the oft-quoted sharply increased risk of uterine cancer in women with an intact uterus on estrogen alone dates back to older studies using doses that were considerably higher than those available in contemporary practice, as well as older methods of patient monitoring. What about the possibility of exploring ways to provide estrogen alone to menopausal women with an intact uterus without exposing them to increased uterine cancer risk? she asked.

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 – nearly 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," said Dr. Coates of the University of Sydney. ■