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This e-newsletter presents reviews of important, recently published scientific articles selected by The North American Menopause Society (NAMS), the leading nonprofit scientific organization dedicated to improving women's health and quality of life through an understanding of menopause. Each has a commentary from a recognized expert that addresses the clinical relevance of the item. Oversight for this e-newsletter issue was by Peter F. Schnatz, DO, Chair-Elect, 2008-2009 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Schnatz. Disclosures are available on request. Past issues of this e-newsletter may be viewed on the NAMS Web site ([www.menopause.org/news.html](http://www.menopause.org/news.html)).

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Late-breaking news with comments by  
Ping Yang, MD, PhD, and Leon Speroff, MD.

## Lung cancer and EPT in the WHI

Chlebowski RT, Schwartz AG, Wakelee H, et al, for the Women's Health Initiative Investigators. Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomized controlled trial. *Lancet* 2009 Sep 18. [Epub ahead of print] **Level of evidence: I.**

This post-hoc analysis of lung cancers diagnosed in the Women's Health Initiative (WHI) trial over the entire follow-up period assessed whether an association exists between estrogen plus progestin (EPT) and increased mortality from lung cancer. Women in the WHI assigned to EPT had a higher risk of cancer post-intervention than women assigned to placebo.

Cancer incidence and mortality for all lung cancer, small cell lung cancer, and non-small cell lung cancer were assessed from data from WHI treatment and post-intervention follow-up of 16,608 postmenopausal women ages 50 to 79 who had been randomly assigned to 0.625 mg conjugated estrogen (CE) plus 2.5 mg medroxyprogesterone acetate (MPA) (n = 8,506) or matching placebo (n = 8,102).

A total of 109 women in the EPT group were diagnosed with lung cancer after a mean of 5.6

years (SD 1.3) of treatment and 2.4 years (SD 0.4) of follow-up, compared with 85 in the placebo group (incidence per year, 0.16% vs 0.13%; hazard ratio [HR], 1.23; 95% CI, 0.92-1.63; *P* = 0.16). In the EPT group, 96 had non-small-cell lung cancer, as compared with 72 assigned to placebo (0.14% vs 0.11%; HR, 1.28; 95% CI, 0.94-1.73; *P* = 0.12).

There were 73 deaths in the EPT group from lung cancer, compared to 40 deaths in the placebo group (0.11% vs 0.06%; HR, 1.71; 95% CI, 1.16-2.52; *P* = 0.01); there were more deaths from non-small cell lung cancer in the EPT group (62 vs 31 deaths; 0.09% vs 0.05%; HR, 1.87; 95% CI, 1.22-2.88; *P* = 0.004). For small cell lung cancer, incidence and mortality rates were similar.

The conclusion of this post-hoc analysis was that EPT in postmenopausal women increased the number of deaths from lung cancer, particularly from non-small cell lung cancer, which should be included in risk-benefit discussions with women considering EPT.

**Comment #1.** This post-hoc analysis could be considered flawless in terms of its design and how it was conducted. The results are important in two ways: first, women taking EPT should note another potential adverse

effect; and second, they should be aware that there is not a significantly higher risk of developing lung cancer for EPT users. Instead, there is a significantly higher risk of *dying* from lung cancer.

It is no surprise that many readers may find these results somewhat confusing or counter-intuitive because of a few inherent shortcomings of this type of analysis. It was based on a treatment trial not designed to answer the question of interest, specifically, incidence and mortality of lung cancer. There are three shortcomings that cause some uncertainty regarding the results reported by Chlebowski et al:

1. Some of the women may have had asymptomatic lung cancer upon entering the original trial, which could have been identified by CT scan (or other workup for detecting lung cancer).
2. Because cigarette smoking is such a profound cause of lung cancer, residual confounding effects still remain even after matching on smoking status and categories of intensity (pack/day) and duration (years smoked). It would be helpful to compare the smoking history between the two groups; particularly, intensity and duration of current smokers versus former smokers.
3. Looking at the disease stage and histology carefully, it is apparent that the significant difference between the EPT and placebo groups was for metastatic lung cancer (many of those with unspecified histology). One explanation is that there were existing lung cancers that progressed during the follow-up time, therefore a coincidence (chance finding); or, EPT may be related to the aggressiveness or progression of the cancer. This second hypothesis needs further evidence.

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**Comment #2.** The leading cause of cancer mortality in American women and men is lung cancer; 87% of the deaths occur in smokers and there are twice as many deaths in women as with

breast cancer annually.<sup>1</sup> In this post-hoc analysis that combined data from 0 to 4 years of follow-up with the treatment period in the canceled EPT arm of the WHI, the incidence of non-small cell lung cancer (the type that accounts for about 80% of lung cancer) was nonsignificantly increased; but the number of deaths and the number of poorly differentiated and metastatic tumors increased in the treatment group. The cases were essentially limited to past and current smokers and to women over age 60. Although the WHI was not designed to assess lung cancer, and chest imaging was not part of the study protocol, the results are provocative and concerning.

There is reason to believe that lung cancer might be a target tissue for estrogen; at the same time, there is evidence to indicate that the impact is not detrimental, but protective. Estrogen receptors are present in normal and non-small cell lung cells;<sup>2</sup> however, case-control studies have indicated a decreased risk for lung cancer, and specifically non-small cell tumors.<sup>3-7</sup> Two studies even found a protective effect in hormone users against lung cancer especially in smokers.<sup>8,9</sup> The Nurses' Health Study found an increase in lung cancer mortality in women who underwent early bilateral oophorectomy and did *not* use estrogen.<sup>10</sup> Despite these encouraging findings, gene expression is stimulated in non-small cell lung cancer cells by estrogen, and proliferation of these cells is reduced by an estrogen antagonist.<sup>11,12</sup>

The editorial that accompanied this report by Ganti, an oncologist who had previously reported decreased survival in women with lung cancer who used hormone therapy (HT),<sup>13</sup> concludes that these results "seriously question whether hormone-replacement therapy has any role in medicine today." The editorial conveniently ignores the lack of lung cancer impact in nonsmokers and in women under age 60, as well as in the WHI reports indicating protection against coronary heart disease in younger postmenopausal women. Furthermore, in contrast to Ganti's editorial, others have not

detected a decreased survival in lung cancer patients who have used HT.<sup>14,15</sup>

The overall data, including the WHI analysis, suggest that initiating EPT in older women with a history of smoking may promote the growth of existing lung cancers. The WHI evidence in women under age 60 is reassuring, and case-control and cohort data that reflect hormone use in a younger population than in the WHI indicate that estrogen is associated with some protection against lung cancer.

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The level of evidence indicated for each study is based on a grading system that evaluates the scientific rigor of the study design, as developed by the US Preventive Services Task Force. A synopsis of the levels is presented below.

Level I	Properly randomized, controlled trial.
Level II-1	Well-designed controlled trial but without randomization.
Level II-2	Well-designed cohort or case-control analytic study.
Level II-3	Multiple time series with or without the intervention (eg, cross-sectional and uncontrolled investigational studies).
Level III	Meta-analyses; reports from expert committees; descriptive studies and case reports.

### 2010 Call for Abstracts

Don't miss the opportunity to submit your research abstracts to NAMS for presentation at the 21st Annual Meeting (October 6-9, 2010) in Chicago, IL.

- Submit your abstracts through the NAMS Web site:  
[www.menopause.org](http://www.menopause.org)
- Information submitted for consideration must not be identical to that presented at any meeting prior to the NAMS meeting, and the study must have been published as of April 30, 2010
- The abstract submission deadline is April 30, 2010
- Top abstracts will be accepted for oral presentation and up to four poster prizes will be awarded (top prize: \$1,000)
- All accepted abstracts will be published in the NAMS journal, *Menopause*, after the meeting

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