Original Study

Estrogen Plus Progestin and Lung Cancer: Follow-up of the Women's Health Initiative Randomized Trial

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Abstract

In the Women's Health Initiative randomized trial evaluating estrogen plus progestin after 5.6 years' intervention and 8 years' cumulative median follow-up, there were more lung cancer deaths in the hormone-treated group ($P = .01$). Now, after 6 years' additional postintervention follow-up, the increase in lung cancer deaths was found to be attenuated (linear trend for difference over time, $P = .042$).

Introduction: In the Women's Health Initiative (WHI) estrogen plus progestin trial, after 5.6 years' intervention and 8 years' median follow-up, more women died from lung cancer in the hormone therapy group (hazard ratio [HR], 1.71; 95% confidence interval [CI], 1.16-2.52; $P = .01$). Now after 14 years' median follow-up, we reexamined combined hormone therapy effects on lung cancer mortality. **Patients and Methods:** In the WHI placebo-controlled trial, 16,608 postmenopausal women aged 50 to 79 years and with an intact uterus were randomly assigned to once-daily 0.625 mg conjugated equine estrogen plus 2.5 mg medroxyprogesterone acetate (n = 8506) or placebo (n = 8102). Incidence and mortality rates for lung cancer were assessed from multivariant proportional hazard models. **Results:** After 14 years' cumulative follow-up, there were 219 lung cancers (0.19% per year) in the estrogen plus progestin group and 184 (0.17%) in the placebo group (HR, 1.12; 95% CI, 0.92-1.37; $P = .24$). While there were more deaths from lung cancer with combined hormone therapy (153 [0.13%] vs. 132 [0.12%], respectively), the difference was not statistically significant (HR, 1.09; 95% CI, 0.87-1.38; $P = .45$). The statistically significant increase in deaths from lung cancer observed during intervention in women assigned to estrogen plus progestin was attenuated after discontinuation of study pills (linear trend over time, $P = .042$). **Conclusion:** The increased risk of death from lung cancer observed during estrogen plus progestin use was attenuated after discontinuation of combined hormone therapy.

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Introduction

In the Women's Health Initiative (WHI) clinical trial evaluating estrogen plus progestin in postmenopausal women, after a median 5.6 years' intervention and 8.0 years' cumulative follow-up, there were 23% more lung cancers in the combined hormone therapy group, a nonsignificant difference ($P = .16$). However, more women died from lung cancer in the combined hormone therapy group (73 [yearly incidence 0.11%] vs. 40 [0.06%]; hazard ratio [HR], 1.71; 95% confidence interval [CI], 1.16-2.52; $P = .01$).[1] In the WHI trial evaluating estrogen alone in postmenopausal women with prior hysterectomy, no effect on lung cancer incidence or outcome was observed.[2] Findings from these trials led to the

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hypothesis that estrogen plus progestin adversely influences lung cancer outcome.

Results from observational studies of menopausal hormone therapy and lung cancer incidence have been mixed, with lower risk,[3-5] no effect,[6,7] and increased risk[8,9] reported. However, 2 recent meta-analyses have associated hormone therapy use with significantly lower lung cancer incidence.[10,11]

Against this background, when the WHI clinical trial was updated after a median cumulative follow-up of 13 years, estrogen plus progestin did not influence lung cancer incidence (HR, 1.10; 95% CI, 0.89-1.35).[12] In that report, deaths from and after lung cancer and findings by histology and smoking status were not reported. Therefore, we conducted analyses to determine whether the adverse effect of estrogen plus progestin on deaths from lung cancer observed during the intervention[1] persisted during long-term postintervention follow-up.

Materials and Methods

Participants and Outcomes

The design of the WHI hormone therapy trial evaluating estrogen plus progestin has been described elsewhere.[13,14] Postmenopausal women aged 50 to 79 years with an intact uterus were entered from 40 clinical centers in the United States from 1993 to 1998. Not eligible were women with previous breast cancer, any other cancer within 10 years except for nonmelanoma skin cancer, or women with an anticipated survival of less than 3 years. Menopausal hormone therapy users required a 3-month washout before entry. The trial was approved by institutional review boards at each clinical center, and participants provided written informed consent. Information on demographic and other variables, including tobacco use, was collected using standard questionnaires. Medication use was collected by interview and review of medication containers. Clinical outcome information was collected at 6-month intervals through March 2005 and then annually.

The primary study efficacy outcome was coronary heart disease, with a calculated sample size of 15,125 based on anticipated 21% risk reduction.[13] The primary safety outcome was invasive breast cancer. Other primary end points as a component of a monitoring global index included stroke, hip fracture, pulmonary emboli, colorectal cancer, endometrial cancer, and death from any cause. Although lung cancer was not a predefined study outcome, reports of lung cancer were confirmed, initially at the clinical centers by centrally trained physician adjudicators after medical record review. Final adjudication was conducted at the WHI Clinical Coordinating Center using the Surveillance, Epidemiology and End Results coding system.[15] Attribution of cause of death was based on medical record and death certificate review (Seattle, WA, USA). Linkage to the National Death Index was conducted serially.

Randomization and Masking

Women were randomly allocated to daily combined conjugated equine estrogens (0.625 mg/day) plus medroxyprogesterone acetate (2.5 mg/day) tablets (Prempro; Wyeth-Ayerst, Collegeville, PA, USA) or an identical-appearing placebo using a computerized permuted block algorithm stratified by age and randomization in the WHI dietary modification trial. Double-blind study drug dispensing utilized a secured database system and was implemented by the Clinical Coordinating Center (Seattle, WA, USA). Participants and clinical center physicians and staff were blinded to the randomization group, with unblinding only if needed to manage adverse events. Chest imaging was not protocol defined, and medical decisions regarding pulmonary findings were directed by community physicians.

Procedures

After 5 to 6 years (median), the intervention was ended when more risks than benefits with estrogen plus progestin were identified; participants were instructed to discontinue study drugs on July 8, 2002.[13] Follow-up per protocol continued through March 31, 2005, the original trial termination date. Subsequent follow-up required reconsent, which was obtained from 12,788 participants, 83% of those surviving. The participant flow has been described elsewhere[12] and is provided as a CONSORT diagram (Supplemental Figure 1 in the online version).

Statistical Analyses

Results for lung cancer incidence and deaths from lung cancer (those directly attributed to lung cancer) and deaths after lung cancer (regardless of cause) were assessed with time-to-event methods based on the intention-to-treat principle, which included all 16,608 randomized participants. Event times were defined relative to the randomization date. Cancer incidence rate comparisons are presented as HRs and 95% CIs from Cox proportional hazard models stratified by age, history of lung cancer, and randomization group in the WHI dietary modification trial.

Time-varying HRs were calculated and plotted, with the use of the same regression model adjustments as those listed above. The models fit a smooth, nonparametric HR over the entire follow-up period. In addition, the time-varying HRs were estimated separately in the intervention and postintervention periods, and a test for a linear trend in each phase performed. Analyses were conducted for all lung cancers and lung cancer deaths.

Subgroup analyses (smoking status, age at study entry [decade], and previous hormone use) were examined in Cox proportional hazard models with P values from Wald χ^2 statistics. Because 3 subgroups were examined, less than 1 statistically significant interaction was expected by chance alone. Additional sensitivity analysis adjusted for adherence, censoring women 6 months after they became nonadherent (defined as consuming $< 80\%$ of study pills or initiating nonprotocol hormone therapy), incorporating time-varying weights, inversely proportional to the estimated probability of remaining adherent.

A level of .05 was used for assessing the statistical significance of P values in all analyses. SAS 9.3 1 for Windows (SAS Institute, Cary, NC, USA), and R 2.15 (R Development Core Team, http://www.R-project.org/), were used for all analyses. All statistical tests were 2-sided. This study was registered with ClinicalTrials.gov (NCT00000611).

The study sponsor had input into the design and conduct of the study and participated in the review but not in the preparation of the report. The corresponding author had full access to all the study data and had final responsibility to submit the document for publication.