Hormone Use, Reproductive History, and Risk of Lung Cancer

The Women's Health Initiative Studies

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Introduction: Results from the Women's Health Initiative clinical trials demonstrated no increase in the risk of lung cancer in postmenopausal women treated with hormone therapy (HT). We conducted a joint analysis of the Women's Health Initiative observational study data and clinical trials data to further explore the association between estrogen and estrogen-related reproductive factors and lung cancer risk.

Methods: Reproductive history, oral contraceptive use, and postmenopausal HT were evaluated in 160,855 women with known HT exposures. Follow-up for lung cancer was through September 17, 2012; 2467 incident lung cancer cases were ascertained, with median follow-up of 14 years.

Results: For all lung cancers, women with previous use of estrogen plus progestin of less than 5 years (hazard ratio = 0.84; 95% confidence interval = 0.71–0.99) were at reduced risk. A limited number of reproductive factors demonstrated associations with risk. There was a trend toward decreased risk with increasing age at menopause (p_{trend} = 0.04) and a trend toward increased risk with increasing number of live births (p_{trend} = 0.03). Reduced risk of non–small-cell lung cancer was associated with age 20–29 years at first live birth. Risk estimates varied with smoking history, years of HT use and previous bilateral oophorectomy.

Conclusions: Indirect measures of estrogen exposure to lung tissue, as used in this study, provide only weak evidence for an association between reproductive history or HT use and risk of lung cancer. More detailed mechanistic studies and evaluation of risk factors in conjunction with estrogen receptor expression in the lung should continue as a role for estrogen cannot be ruled out and may hold potential for prevention and treatment strategies.

Key Words: Lung cancer, Hormone therapy, Reproductive history.

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In 2013, an estimated 110,110 women in the US were diagnosed with lung cancer and 72,220 died from this disease.[1] There remains a gender gap in incidence rates with men having higher rates than women, but with the declining incidence among men and the leveling off of incidence among women only recently, this gender difference is narrowing. The lifetime risk of developing lung cancer is 6.9% in both men and women.[1]

While approximately 90% of lung cancer deaths are attributable to cigarette smoking in men, only 75–80% of lung

cancer deaths in women are attributable to smoking.[2] There has been considerable debate about differences in lung cancer occurrence and characteristics between men and women. Women are more likely to have adenocarcinomas of the lung (45.0%) than men (37.2%) and are more likely to have tumors with *EGFR* mutations.[3] Women who never smoked are also more likely to develop lung cancer than men who have never smoked.[4–7] However, the 5-year relative survival after a lung cancer diagnosis is better for women than for men (20.0% and 15.4%, respectively).[1] Taken together, male–female differences in lung cancer risk, tumor characteristics and outcome have fueled investigations into the role of estrogens in lung cancer risk and prognosis.

Epidemiologic studies of estrogen as a risk factor for lung cancer have focused on reproductive and estrogen use history. Findings have been inconsistent, with reports of increased and decreased risk associated with postmenopausal hormone therapy (HT), oral contraceptive (OC) use, pregnancy, and menstrual history.[8–31] The Women's Health Initiative (WHI) clinical trials (CTs) data demonstrated that neither the use of estrogen plus progestin or estrogen alone was associated with lung cancer incidence.[18,19] Taken as a whole, inconsistent findings across studies are likely due to a number of factors including variations in HT dosing over time and potential misclassification of exposures, however, they suggest a possible role for exogenous estrogens (i.e., HT, OCs) in the development of lung cancer.

We evaluated the role of reproductive factors and hormone use in determining risk of lung cancer in women from both the Women's Health Initiative Observational Study and CTs.

METHODS

The Women's Health Initiative

The WHI enrolled a geographically and ethnically diverse cohort of 161,808 postmenopausal women age 50–79 years between October 1, 1993 and December 31, 1998 at 40 centers across the United States. All participants provided informed consent. Women were enrolled in one of four randomized CTs testing use of estrogen alone or estrogen plus progestin, calcium plus vitamin D (CaD), or low fat diet (dietary modification—DM) on several outcomes. In addition, the observational study (OS) enrolled women who provided detailed lifestyle and medical history and were followed for disease outcomes. Details of recruitment[32] and baseline characteristics of study participants[33] have been published previously. Reproductive history (age at first birth, number of pregnancies, age at menarche, age at menopause, bilateral oophorectomy), use of unopposed estrogens, estrogen plus progesterone, and/or OCs (never used, duration of use <5, 5–9, 10–14, 15+ years) were collected at the baseline clinic visit by self-report. Current users of HT were defined as women using HT at baseline in the OS, or women using HT at baseline in the DM or CaD trials (who were not participating in the HT trial) or women assigned to HT use in the HT CT. Past users of HT were defined as women not using HT at baseline in the OS, DM, or CaD CTs but who had used HT in the past, women receiving placebo in the HT CT but who had used HT in the past, or women randomized to HT who used HT in the past and completed a wash out period before going on trial. Never users of HT were defined as women never using HT in the OS or non-HT CTs or women on the placebo arm of the HT CT who had never used HT before trial initiation. Therefore, any of the participants, even those enrolled in the HT CT and randomized to HT, could have been defined as past users of HT.

The type of HT was classified as that reported at baseline for all women except for those on the intervention arm of the HT CT, for whom the assigned HT was used. Duration of use was calculated from start of use to before baseline or randomization. Self-report of age at enrollment, education, income, smoking status (never smoked more than 100 cigarettes, ever smoked more than 100 cigarettes), number of cigarettes smoked per day (<5, 5–14, 15–24, 25–34, 35–44, 45+), years smoked (<5, 1–9, 10–19, 20–29, 30–39, 40–49, 50+), age started smoking in 5-year intervals, age quit smoking in 5-year intervals, passive smoke exposure as a child and as an adult (home and work), alcohol intake, physical activity, diet and medical history were obtained at baseline.

Study participants were followed annually in the OS, and biannually through 2005 and annually thereafter in the CTs. At each follow-up, additional questionnaire data were obtained including self-report of cancer. Self-reports of cancer were confirmed by review of medical records and pathology reports. As of September 17, 2012, 2467 lung cancers had been reported and centrally adjudicated. Of these, 2220 were classified as non–small-cell lung cancers (NSCLC), 236 were classified as small-cell lung cancers (SCLC) and 11 had missing histology.

Statistical Approach

The baseline subject questionnaire data, supplemented with data on lung cancer incidence, were used in the analysis. The primary objective of this study was to assess the association of reproductive history and use of OCs and HT, after adjustment for tobacco use and other known lung cancer risk factors, with risk of lung cancer among women. Two hundred fifty-seven women who reported a history of lung cancer on the baseline questionnaire were excluded. In addition, 696 women who were enrolled in the WHI studies but for whom there was no follow-up information were also excluded, leaving 160,855 women in this analysis, with 2467 incident cases of lung cancer.

Associations between reproductive and hormonal factors and lung cancer incidence were assessed using Cox regression models to compute adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). Time to incident lung cancer was computed as days from randomization in the CTs or enrollment in the OS to the first diagnosis of lung cancer during follow-up. Otherwise, follow-up was censored at the last documented follow-up contact, death, or September 17, 2012, whichever came first. Additional analyses were conducted, stratified by baseline smoking status (never, former, current) and in relation to risk by lung cancer histology (SCLC, NSCLC, and specific NSCLC subtypes). For the analyses of histology subtype, each subtype was treated as a

