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HORMONE USE, REPRODUCTIVE HISTORY AND RISK OF LUNG CANCER: THE WOMEN'S HEALTH INITIATIVE STUDIES

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ABSTRACT

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

Methods: Reproductive history, oral contraceptive (OC) use, and postmenopausal hormone therapy (HT) was evaluated in 160,855 women with known HT exposures. Follow-up for lung cancer was through September 17, 2012; 2,467 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 < 5 years (HR=0.84; 95% CI 0.71-0.99) were at reduced risk. A limited number of reproductive factors demonstrated associations with risk. There was a trend towards decreased risk with increasing age at menopause (p_{trend}=0.04) and a trend towards 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 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 ER expression in the lung should continue as a role for estrogen can't be ruled out and may hold potential for prevention and treatment strategies.

Key Words: Lung Cancer, Hormone Therapy, Reproductive History

Introduction

In 2013, an estimated 110,110 women in the U.S. 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 post-menopausal hormone therapy (HT), oral contraceptive (OC) use, pregnancy and menstrual history [8-31]. The Women's Health Initiative (WHI) clinical trials 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 (WHIOS) and Clinical Trials (CTs).

Methods

The Women's Health Initiative

The WHI enrolled a geographically and ethnically diverse cohort of 161,808 post-menopausal 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 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 oral contraceptives (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 hormone therapy (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, 2,467 lung cancers had been reported and centrally adjudicated. Of these, 2,220 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 oral contraceptives and hormone therapy, 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 2,467 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

separate outcome and lung cancer cases of a different subtype were censored at the time of diagnosis.

Each baseline hormonal or reproductive factor was modeled separately in relation to disease outcome. Tests for trend were performed by modeling the continuous form of the variable if it was originally collected; otherwise, a linear trend was evaluated by modeling the integer-scored categorical variable as a continuous variable. A set of covariates was selected, a priori, for adjustment of potential confounding, including age at enrollment/recruitment (continuous), race/ethnicity (white, black, other), education (less than high school, high school degree/GED, education after high school, college degree or higher), U.S. region (Northeast, South, Midwest, West), pack-years of smoking (never smoked, <5, 5 to <20, ≥20), family history of cancer, personal history of asthma or emphysema, and body mass index (BMI) (<25, 25 to <30, ≥30). The baseline hazard function in the Cox model was stratified by age (5-year groups); hormone therapy trial randomization assignment or study enrollment (active conjugated equine estrogen [CEE] plus medroxyprogesterone acetate [MPA], placebo CEE and MPA, active CEE, placebo CEE, or not randomized), dietary modification trial randomization (intervention, control, or not randomized), CaD trial, or OS enrollment; hysterectomy status at baseline; and extension study participation.

Associations were evaluated in a multivariable model that included statistically significant covariates and risk factors. Several variables were not retained in the final multivariable model because their inclusion made no important changes to risk estimates or their interpretation. These included age at menarche, number of births,

history of asthma, age at menopause, years since menopause, duration of past oral contraceptive use, and duration of prior unopposed estrogen use.

Statistical tests were two-sided, and p values less than 0.05 were considered statistically significant. All analyses were performed using the SAS system, version 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

Table 1 presents the baseline characteristics of the 160,855 women included in the analysis stratified by lung cancer status. In the entire cohort, 2,467 lung cancers were diagnosed during follow-up. After adjustment for multiple factors (see Methods and footnote on Table 2), the only variables in which there was a statistically significant relationship with lung cancer risk overall, and NSCLC specifically, included later age at first live birth and later age at menopause, both of which were associated with a reduced risk. Increasing time since menopause was associated with an increased risk (Table 2).

The only statistically significant findings with regard to hormone use were a reduction in risk associated with previous use of estrogen plus progestin of less than 5 years for all lung cancers (HR=0.84; 95% CI 0.72-0.98) and a similar reduction in risk associated with 5 to <10 years of any previous hormone use for NSCLC (HR=0.84; 95% CI 0.71-0.99). Little variation in risk in association with hormone use was seen for subtypes of NSCLC including adenocarcinomas, squamous cell carcinomas, large cell and associated subtypes, and other NSCLC or unspecified NSCLC (data not shown). There were no significant relationships to risk of SCLC.

Table 3 reports the relationship between reproductive factors and lung cancer risk after additional adjustment for all other reproductive and hormone use variables that were significant in any of the lung cancer analyses detailed in Table 2. The results by lung cancer histology are also presented in Table 3. This analysis showed that less than 5 years of previous use of estrogen plus progestin was associated with decreased risk of lung cancer (HR=0.84; 95% CI 0.71-0.99). A similar risk estimate was noted for NSCLC and SCLC, although these findings did not reach statistical significance. There was also a statistically significant decrease in NSCLC incidence among women with a later age at first birth (HR=0.84; 95% CI 0.73-0.98), and for all lung cancers, a trend towards decreased risk with increasing age at menopause (p_{trend}=0.04) and a trend towards increased risk with increasing number of live births (p_{trend}=0.03) was observed.

Multivariable modeling was conducted for smoking status strata as described above (Table 4). Bilateral oophorectomy prior to enrollment was differentially associated with lung cancer risk; risk was increased in never smokers who had undergone bilateral oophorectomy (HR=1.47; 95% HR 1.00-2.16; p=0.049) and decreased in current smokers who had undergone the same procedure (HR=0.68; 95% CI 0.51-0.90). The risk associated with this procedure was intermediate in former smokers (HR=0.92; 95% CI 0.76-1.1)(p_{trend}=0.098). Additionally, among current smokers only, women with 5 or more live births were at 34% increased risk and women with 10 or more years of previous use of estrogen plus progestin were at 62% increased risk, but this trend in risk associated with duration of use was not statistically significant.

Discussion

This study found no consistent contributions to lung cancer risk for a wide range of reproductive history measures. This is an area in which the epidemiologic literature has been inconsistent. Decades ago, studies of adenocarcinoma of the lung reported that early age at menopause was associated with decreased risk [8], and non-significant increases in risk were associated with later age at menarche, surgical menopause or early menopause and hormone use [22]. Other studies have reported no association between lung cancer risk and reproductive factors [12,27], increased risk associated with increased parity [28], or decreased risk with increasing age at first live birth [10]. In cohort studies, adenocarcinoma risk was reduced with late menarche and increased with early age at menopause (including that resulting from bilateral oophorectomy particularly prior to age 40) [16], and overall lung cancer risk was increased in women having 5 or more children, a finding we replicated only among current smokers, while decreased for women giving birth for the first time after age 30 [31]. Boggs et al. report non-significant increased risk of lung cancer in African American women with a history of bilateral oophorectomy before age 40 and fewer than 2 years of hormone use [34]. We found that bilateral oophorectomy was differentially associated with lung cancer risk; risk was increased in never smokers (HR=1.47; 95% HR 1.00-2.16; p=0.049) and decreased in smokers (HR=0.68; 95% CI 0.51-0.90). These findings need further exploration to untangle contributions from the underlying reason for bilateral oophorectomy, age at surgery, hormone use before and after surgery, and timing of cigarette exposure.

Overall, however, published work, like our study, does not support the idea that reproductive history independently contributes to lung cancer risk.

The epidemiologic literature is also inconsistent with regard to the role of hormone use (both HT and OCs) in lung cancer risk. The overall results presented here suggest that OC and HT use are not associated with risk of lung cancer. Only in current smokers do we find increased risk associated with 10 or more years of estrogen plus progestin use. There have been several pooled or meta-analyses of menopausal hormone therapy and risk of lung cancer that included many of the same studies[14,15,21,35]. Of the 11 studies and over 220,000 participants included in the analysis by Oh et al., the pooled estimate of relative risk for lung cancer associated with HT use was 0.87 (95% CI 0.74-1.02), a non-statistically significant reduction in risk [14]. Among cohort studies, the estimated relative risk was 1.01 (95% CI 0.74-1.38), while among case-control studies the estimate was 0.81 (95% CI 0.68-0.97). Of the 11 studies included, one study reported increased risk [8], four studies reported no association [10,12,23,36], and three studies reported decreased risk [11,37,38] associated with HT use. Another meta-analysis of 25 studies showed an OR of 0.91 (95% CI 0.83-0.99) for the association between HT use and lung cancer risk [35], while a pooled analysis of 6 case-control studies reported an OR of 0.77 (95% CI 0.66-0.90) [21]. Several large cohort studies, including the WHI CTs, have reported no association between HT use and incidence of lung cancer [16-19]. The study by Schwartz et al. is the only one to evaluate risk by ER expression in the lung tumors [12]. Decreased risk of estrogen receptor (ER) positive NSCLC was reported in post-menopausal women taking HT (OR=0.42; 95% CI0.24-0.74), with no association seen for ER negative tumors [12]. The WHI did not

include a determination of lung tumor ER receptor expression so it was not possible to evaluate differential effects of hormone use in ER positive versus ER negative lung cancer.

While not a primary analysis topic for this study, an important note is that 55% of the lung cancers were diagnosed among former smokers. We estimated, based on the data available, that 69% of these former smokers had quit smoking more than 15 years before lung cancer diagnosis. This suggests that there is a large population of longer term women former smokers at risk.

This study has several strengths including its prospective nature and large sample size. The prospective design allowed for collection of exposure data before lung cancer diagnosis. However, there were also some limitations. While the CT data provide the best opportunity for understanding the relationship between HT use and lung cancer risk, only a small number of lung cancer cases developed in the CT arms. All study arms collected smoking dose and duration as categorical variables, and therefore did not allow for specific pack-years of exposure to be calculated. This may have resulted in residual confounding within smoking category. The other limitation is not having tumor ER expression data. Estrogen exposure may differentially affect development and/or progression of tumors with specific characteristics. Hormone use data also may not accurately reflect local estrogen level in the lung and therefore null associations between hormone use and lung cancer risk should not rule out the potential for a role of estrogen in lung carcinogenesis. Multiple pathways of estrogen action exist [39-48] and estrogen levels in lung tissue, both from endogenous and

exogenous estrogens, have never been measured, so the role of estrogen in lung cancer risk is still an open question.

In conclusion, this large, prospective study of lung cancer in women did not find strong associations with specific reproductive variables and risk, and provided only weak support for a role of hormone use in the etiology of lung cancer. There remain questions about estrogen and lung cancer risk that will not easily be answered by studies focusing on hormone use. The interplay between cigarette smoking, estrogen, genetic susceptibility and lung cancer is complex and continued study is necessary to tease apart these relationships.

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