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ORIGINAL REPORT

Lung Cancer and Hormone Replacement Therapy: Association in the Vitamins and Lifestyle Study

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ABSTRACT

Purpose
Lung cancer is the leading cause of cancer-related mortality among women. The role of hormone replacement therapy (HRT) in lung cancer development is unclear.

Patients and Methods
We evaluated a prospective cohort of 36,588 peri- and postmenopausal women aged 50 to 76 years from Washington State recruited in 2000 to 2002 (Vitamins and Lifestyle [VITAL] Study). Lung cancer cases (n = 344) were identified through the Seattle-Puget Sound Surveillance, Epidemiology, and End Results cancer registry during 6 years of follow-up. Hazard ratios (HRs) associated with use and duration of specific HRT formulations were calculated for total incident lung cancer, specific morphologies, and cancer by stage at diagnosis.

Results
After adjusting for smoking, age, and other potential confounders, there was an increased risk of incident lung cancer associated with increasing duration of estrogen plus progestin (E+P) use (HR = 1.27 for E+P use 1 to 9 years, 95% CI, 0.91 to 1.78; and HR = 1.48 for E+P use ≥ 10 years, 95% CI, 1.03 to 2.12; *P* for trend = .03). There was no association with duration of unopposed estrogen use. Duration of E+P use was associated with an advanced stage at diagnosis (*P* for trend = .03).

Conclusion
Use of E+P increased the risk of incident lung cancer in a duration-dependent manner, with an approximate 50% increased risk for use of 10 years or longer. These findings may be helpful for informing women of their risk of developing lung cancer and delineating important pathways involved in hormone metabolism and lung cancer.

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INTRODUCTION

Lung cancer is the leading cause of cancer mortality for women in the United States.[1] Tobacco causes 90% of lung cancers,[2] and cessation is the only recommended method for prevention.[3] However, the prevalence of tobacco use remains high,[4] and lung cancer risk persists after smoking cessation.[5] Accordingly, it is important to evaluate additional modalities that affect the risk of incident lung cancer.

Exogenous hormones may impact lung cancer development. The biologic mechanisms underlying hormone metabolism and lung cancer are not clear in direction or magnitude.[6,7] Studies evaluating hormone replacement therapy (HRT) use and incident lung cancer have had conflicting results and many have had limitations such as not examining individual HRT formulations, duration of use, limited adjustment for the confounding effects of tobacco use, and/or limited to nonsmokers.[8-21] There is concern that associations found in observational studies may not be replicated in placebo-controlled trials as shown in trials of both lung cancer chemoprevention and HRT,[22-24] and several trials have suggested that estrogen plus progestin may be associated with an increased risk of lung cancer incidence[25] and death.[26-28]

Given these conflicting findings, studies of HRT and lung cancer should examine the effects of duration and HRT formulation in the association between HRT and lung cancer and adjust for the confounding of smoking to decrease the chances of misconstruing the relationship between HRT and lung cancer.[29] We used the prospective cohort study (Vitamins and Lifestyle [VITAL] study) to evaluate the association of HRT use with incident lung cancer.

PATIENTS AND METHODS

Subjects

The methods used in the VITAL cohort study have been described.[30] From October 2000 to December 2002,

we mailed questionnaires to 168,953 women aged 50 to 76 years who lived in the area covered by the Seattle-Puget Sound Surveillance, Epidemiology, and End Results (SEER) registry, using names from a commercial mailing company. A total of 41,157 women (24.4%) returned the questionnaire, and of those, 820 failed eligibility or quality control checks, leaving 40,337 women. Baseline data included items on medication use, diet, medical history, personal characteristics, and cancer risk factors. The responders were more educated than the general population and smoked less currently, but were similar in body mass index (BMI).[30] The Fred Hutchinson Cancer Research Center's institutional review board approved the protocol.

The censored date was the date of withdrawal from the study, death, move out of the SEER catchment area, or last date of linkage to SEER for diagnosis of lung cancer. Deaths were ascertained by linkage to Washington State death files, and moves out of the area from the National Change of Address System, letters, and telephone calls.

For this report, we excluded participants with a previous diagnosis of lung cancer (n = 176) or for whom this datum was missing (n = 86). We excluded subjects whose lung cancer was identified on a death certificate only or whose lung cancer morphology was lymphoma (n = 4). We then excluded subjects who were not perimenopausal or postmenopausal (n = 1,995). Lastly, we excluded subjects with completely missing information regarding HRT use (n = 1,488), leaving 36,588 women.

Outcome Assessment: Lung Cancer

Participants were observed for lung cancer occurring from baseline through December 31, 2007, through linkage to SEER. SEER has accurate and complete data collection[31] and is reliable for lung cancer histology.[32] If a subject had multiple diagnoses of lung cancer, we used the time to first diagnosis.

Exposure Assessment: HRT Use

Hormone replacement therapy use was ascertained by inquiring about use of prescription estrogen and progestin as pills or patches, excluding oral contraceptives. Information was obtained on hormone therapy use status (never, former, current) and years of use (categorized as ≤ 1, 1 to 4, 5 to 9, 10 to 14, or ≥ 15). Past HRT use for less than 1 year was combined with no use (never). Current HRT use less than 1 year was classified as 1 to 4 years of use. Years of estrogen plus progestin (E+P) use and years of estrogen-only use were computed separately. The reference group was users of neither type of HRT. Women with periods of exposure to both unopposed estrogen and E+P had the relevant years of use included in both analyses. Subjects with estrogen only use were excluded from the duration of E+P use analysis and users of E+P only were excluded from the duration of estrogen use analysis.

Covariates

Tobacco. Smokers were defined as individuals who smoked at least one cigarette per day for at least a year. Smoking status was classified as never, current, quit 10 years or more, or quit less than 10 years ago, as of the date of questionnaire completion. Duration of smoking was estimated by the number of years smoked, intensity was estimated by the usual number of cigarettes smoked per day, and pack-years was computed as years smoked × cigarettes per day/20.

Gynecologic factors. Perimenopausal women were defined as having menses in the past year that were not regular. Women were assumed to be postmenopausal if they had no periods in the year before baseline, had ever used hormone therapy, had had a bilateral oophorectomy, or were ≥ 60 years at baseline. Age at menopause was categorized in 5-year increments (≤ 39 to ≥ 55 years) to the age at which menstrual periods ended or age of first use of hormone therapy or were 60 years old at baseline, whichever came first. Women who reported a hysterectomy without bilateral oophorectomy were considered to be postmenopausal if they had ever used hormone therapy or were ≥ 55 years at baseline. For those women, age at menopause was set to the age at which they first used hormone therapy (if before age 55 years); otherwise, it was set to missing.

Additional covariates. Subjects reported age, race/ethnicity, marital status, and education. Previous history of cancer and self-report of diagnosed chronic obstructive pulmonary disease (COPD) were recorded. We categorized family history as none or at least one first-degree relative with lung cancer. BMI was calculated from the respondent's self-reported current weight and height, measured as kilograms per square meters.

Daily servings of fruit were assessed by a food frequency questionnaire that was an adaptation from the Women's Health Initiative and other studies,[33-35] with the addition of highly supplemented foods. Subjects were extensively queried about use of nonsteroidal anti-inflammatory drugs and supplemental vitamins.

Statistical Analysis

All analyses were performed using STATA SE-9 (StataCorp, College Station, TX). For the main analysis, Cox regression using robust SEs[36] was used to estimate the hazard ratios (HRs) for associations of HRT use categories and lung cancer risk. Age was the time variable with left truncation for age at baseline and censoring (right truncation) as described above. Subjects with missing data on HRT use or other covariates in the model were excluded from analysis. We analyzed four exposure variables: HRT use, analyzed by categories of use (never, former, and current); ever-use of specific formulations of HRT (none, estrogen only, E+P only, and both); duration of use of E+P; and duration of estrogen only. We treated each duration of use category as a continuous trend variable to assess for trends in lung cancer risk, comparing each category with no use.

On the basis previous work, we used a model that adjusts for confounding by cigarette smoking that included years smoked, pack-years, and a squared pack-years term.[37] We decided a priori to include age, nonwhite race/ethnicity, history of cancer, family history of lung cancer, COPD, BMI (categoric, including missing as a category), age at menopause (categoric, including missing as a category), and hysterectomy/oophorectomy status. We evaluated whether other factors associated with lung cancer risk (nonsteroidal anti-inflammatory drug use, supplemental vitamin E, education, and daily servings of fruit) individually confounded the association of HRT use with lung cancer in the adjusted model. None changed the point estimates of the HRT variables by more than 10% or the 5% level of significance so were not included.

We examined whether the associations of HRT with incident lung cancer use differed by morphology by treating each morphology as a separate outcome, exclusive of the other morphologies, compared with subjects who did not develop lung cancer. We also looked for differences of the HRT–lung cancer associations by smoking status and BMI subgroups. Because few never smokers developed lung cancer, we did not include this group in the stratified smoking status analyses. Likelihood ratio tests were conducted to assess the interaction between HRT use, analyzed as trend variables, and the subgroups. *P* values for interaction were obtained to compare the fit of the models with the interaction terms and without them. Finally, we examined whether the associations of HRT with incident lung cancer use differed by local versus regional/advanced/unknown stage at diagnosis by treating these stages as separate outcomes, exclusive of the other stages, compared with subjects who did not develop lung cancer. Unknown stage was combined with the latter groups because staging information is often missing in advanced cases that are not candidates for surgery. *P* values less than .05 were considered statistically significant.

RESULTS

A total of 36,588 subjects met inclusion criteria and were observed for a mean of 5.9 years (standard deviation = 1.2 years). Three hundred forty-four patients developed lung cancer. Non–small-cell lung cancer (NSCLC) accounted for 77.0% of the total: adenocarcinoma (n = 141 [41.0%]), squamous cell (n = 47 [13.7%]), large cell (n = 9 [2.6%]) and NSCLC, not otherwise specified (n = 68 [19.8%]). Small-cell lung cancer (SCLC) accounted for 12.5% of the total lung cancers. Other lung cancers, mostly comprising carcinomas not otherwise specified and carcinoid/neuroendocrine tumors, accounted for 10.5% of the total. Seventy-three subjects (21.2%) were diagnosed with a local stage

Table 1. Characteristics of Cohort Stratified by Formulation of Hormone Replacement Therapy Use

Characteristic	Overall Cohort (N = 36,588)		No HRT Use		E Use Only		E+P Use Only		Use of Both	
	No.	%	No.	%	No.	%	No.	%	No.	%
Age, years										
Mean	62.4		62.8		63.1		59.5		65.0	
SD	7.3		7.9		7.3		6.0		6.3	
Smoking status										
Never smoker	20,141	55.4	6,750	57.5	5,894	54.0	4,969	56.1	2,149	51.5
Quit ≥ 10 years	11,150	30.7	3,298	28.1	3,393	31.1	2,803	31.6	1,477	35.4
Quit < 10 years	2,166	6.0	614	5.2	739	6.8	501	5.7	273	6.6
Current smoker	2,899	8.0	1,084	9.2	899	8.2	592	6.7	271	6.5
Pack-years*										
Mean	22.9		23.7		23.7		20.0		23.5	
SD	21.6		21.9		22.2		19.7		21.9	
Years smoked*										
Mean	22.7		23.6		23.7		19.9		23.3	
SD	13.9		14.4		13.8		13.0		13.7	
Race/ethnicity										
White	33,395	93.3	10,539	91.4	10,054	93.6	8,291	94.3	3,935	95.6
Socioeconomic variables										
Married	23,973	67.1	7,143	62.1	7,319	68.4	6,245	71.4	2,856	69.4
College graduate or higher	12,134	33.9	3,927	34.1	2,765	25.8	3,969	45.2	1,348	32.8
Medical history										
Cancer	5,981	16.4	2,310	19.5	1,879	17.1	1,029	11.6	647	15.4
COPD	1,450	4.0	428	3.6	559	5.1	232	2.6	192	4.6
Family history of lung cancer†	4,730	13.1	1,451	12.5	1,593	14.7	1,030	11.7	570	13.7
BMI, kg/m^2										
Underweight (≤ 18.5)	495	1.5	177	1.6	135	1.3	114	1.3	55	1.4
Normal (18.5-24.9)	13,556	39.7	4,052	37.4	3,830	37.2	3745	44.2	1,726	43.5
Overweight (25-29.9)	11,484	33.6	3,544	32.7	3,574	34.7	2,796	33.0	1,378	34.8
Obese (≥ 30)	8,623	25.2	3,068	28.3	2,762	26.8	1,822	21.5	806	20.3
Gynecologic factors										
Hysterectomy status										
None	21,714	59.4	9,493	80.3	1,238	11.3	8,219	92.3	2,552	60.8
Hysterectomy	8,208	22.4	1,565	13.2	5,434	49.4	271	3.0	682	16.2
Oophorectomy	201	0.6	67	0.6	56	0.5	48	0.5	25	0.6
Hysterectomy/oophorectomy	6,465	17.7	702	5.9	4,267	38.8	366	4.1	942	22.4
Age at menopause, years										
≤ 39	3,640	10.9	487	5.2	2,239	21.4	193	2.2	607	14.6
40-44	4,934	14.8	896	9.5	2,364	22.6	718	8.2	868	20.9
45-49	9,862	29.6	2,401	25.5	3,093	29.6	2,824	32.4	1,366	32.9
50-54	12,870	38.6	4,582	48.7	2,556	24.4	4,362	50.0	1,172	28.2
≥ 55	2,052	6.2	1,042	11.1	210	2.0	629	7.2	143	3.4

NOTE. Percentages are of nonmissing data and are for the overall cohort and for each formulation of HRT use category. Numbers may not sum to 100% secondary to rounding and missing data. Less than 5% of the overall cohort had missing data except for the following with percentages listed for each category of BMI (7.1%) and age at menopause (9.7%). A total of 1.8% of the overall cohort was missing information on the formulation of HRT used and not included in this summary table.

Abbreviations: HRT, hormone replacement therapy; E, unopposed estrogen; E+P, estrogen plus progestin; SD, standard deviation; COPD, chronic obstructive pulmonary disease; BMI, body mass index.

*Among current or former smokers.

†First-degree relative with lung cancer.

at diagnosis, 97 (28.2%) regional, 164 (47.7%) distant, and 10 (2.9%) had an unknown stage.

When stratified by the formulation of HRT used, the subjects were similar in most respects (Table 1). The E+P only users were somewhat younger with fewer pack-years and years of smoking. This group also had a smaller percentage with a history of cancer but a higher percentage without a hysterectomy.

After adjustment, current and former use of HRT was associated with a nonsignificantly elevated risk of incident lung cancer (HR = 1.23, 95% CI, 0.92 to 1.66; and HR = 1.18, 95% CI, 0.86 to 1.63, respectively; Table 2). Compared with no use of HRT, use of the estrogen plus progestin formulation only was associated with an increased risk of incident lung cancer (HR = 1.47; 95% CI, 1.06 to 2.04). Use of unopposed estrogen only and use of both formulations were not associated with lung cancer.

There was evidence of a dose response associated with the duration of E+P use. Use of E+P for ≥ 10 years was associated with an increased risk of lung cancer compared with no use of HRT (HR = 1.48; 95% CI, 1.03 to 2.12; *P* for trend = .03). Conversely, there was no association between duration of estrogen use and lung cancer.

Table 2. Hazard Ratios for the Association of Hormone Replacement Therapy Use With Incident Lung Cancer

HRT Variable	Noncases (n = 36,244) No.	%	Cases (n = 344) No.	%	Age-Adjusted HR	95% CI	Adjusted HR*	95% CI
HRT status								
Never user	11,642	33.5	104	31.1	Ref		Ref	
Former user	5,668	16.3	73	21.9	1.24	0.92 to 1.68	1.18	0.86 to 1.63
Current user	17,451	50.2	157	47.0	1.13	0.88 to 1.45	1.23	0.92 to 1.66
HRT formulation								
No use	11,723	32.9	104	31.1	Ref		Ref	
E use only	10,878	30.6	117	35.0	1.19	0.92 to 1.57	1.04	0.73 to 1.48
E+P use only	8,840	24.8	64	19.2	1.13	0.82 to 1.10	1.47	1.06 to 2.04
Use of both	4,152	11.7	49	14.7	1.16	0.82 to 1.86	1.24	0.86 to 1.79
Duration								
E+P†								
No HRT use	11,723	47.4	104	47.9	Ref		Ref	
1-9 years	8,688	35.2	59	27.2	1.03	0.75 to 1.42	1.27	0.91 to 1.78
≥ 10 years	4,304	17.4	54	24.9	1.29	0.92 to 1.81	1.48	1.03 to 2.12
P for trend‡					.17		.03	
E use§								
No HRT use	11,723	51.9	104	47.1	Ref		Ref	
1-9 years	3,972	17.6	37	16.7	1.31	0.89 to 1.91	1.14	0.73 to 1.78
≥ 10 years	6,906	30.6	80	36.2	1.15	0.86 to 1.54	0.87	0.56 to 1.34
P for trend					.31		.53	

NOTE. Percentages are of nonmissing data. All HRT variables had less than 2% missing data. Numbers may not sum to 100% secondary to rounding and missing data.

Abbreviations: HRT, hormone replacement therapy; HR, hazard ratio; Ref, reference; E, unopposed estrogen; E+P, estrogen plus progestin.

*Adjusted for age, pack-years, pack-years squared, years smoked, personal history of cancer, family history of lung cancer, chronic obstructive pulmonary disease, body mass index (categorical, including missing as a category), age at menopause (categorical, including missing as a category), hysterectomy type, and nonwhite race/ethnicity.

†Years of E+P use alone. Reference group is subjects who never used any form of HRT. Users of E only are excluded from the analysis.

‡*P* for trend analyses by continuous categories.

§Years of E use alone. Reference group is subjects who never used any form of HRT. Users of E+P only are excluded from the analysis.

When we stratified the analysis by NSCLC and SCLC, no status, formulation, or duration of HRT use was statistically significantly associated with either morphology, though all except estrogen use for ≥ 10 years were associated with increased risks (Table 3). No category of HRT use, formulation, or duration was significantly associated with adenocarcinoma when this morphology was analyzed separately (data not shown).

There was no clear evidence of effect modification by either smoking status or BMI. No category of HRT use, formulation, or duration was significantly associated with incident lung cancer when stratified by smoking status or BMI categories (data not shown).

No HRT use, formulation, or duration category was significantly associated with local stage at diagnosis (Table 4). However, E+P use (HR = 1.52; 95% CI, 1.06 to 2.19; $P = .04$) was associated with more advanced stages, and increasing duration of E+P use was associated as well (P for trend = .03). Unopposed estrogen use and duration were not associated with advanced stages at diagnosis.

DISCUSSION

The use of E+P was associated with an increased risk of incident lung cancer in this study. Although HRT use has declined[38] and is not recommended except for short-term treatment of menopausal symptoms,[39] our results indicate millions of women may remain at risk of developing lung cancer. We found that the association of HRT with lung cancer was duration dependent, with the highest risk for users of E+P ≥ 10 years. Use of E+P was also associated with an advanced stage at diagnosis in a duration-dependent manner. We do not have the power to estimate a safe length of HRT use.

There were not large differences in the associations between NSCLC and SCLC. Similarly, smoking status did not seem to modify the associations. A recent cohort study that also showed increased risks of lung cancer associated with HRT use did not see differences in the association with regard to histology and smoking status.[11] Although obesity may modify the association between HRT and lung cancer,[21] BMI was not an effect modifier in our study. The relatively small number of cases in each subcategory limits our ability to detect differences.

Previous studies of the association between HRT and lung cancer have been mixed.[8-21] In the Cancer Prevention Study II, current use of any HRT was associated with a decreased risk of lung cancer (relative risk = 0.76; 95% CI, 0.62 to 0.92) that was not duration dependent and did not differ by formulation.[9] A case-control study found a duration-dependent decreased risk for lung cancer with HRT use (odds ratio = 0.88; 95% CI, 0.78 to 1.00 for each duration quartile) and did not differ by formulation.[20] Another case-control study reported protective associations with HRT use that did not differ between unopposed estrogen and E+P.[18] Women in the Canadian National Breast Screening Study using HRT (formulation not specified) for 10 years or longer, however, had an elevated risk (HR = 1.51; 95% CI, 1.14 to

Table 3. Hazard Ratios for the Association of Hormone Replacement Therapy Use With Incident Lung Cancer Stratified by Morphology

	NSCLC (n = 265)		SCLC (n = 43)	
HRT Variable	HR	95% CI*	HR	95% CI*
HRT status				
Never user	Ref		Ref	
Former user	1.07	0.74 to 1.56	1.48	0.60 to 3.69
Current user	1.16	0.82 to 1.63	2.15	0.95 to 4.87
HRT formulation				
No use	Ref		Ref	
E use only	1.03	0.68 to 1.55	2.10	0.85 to 5.16
E+P use only	1.22	0.83 to 1.79	1.65	0.58 to 4.70
Use of both	1.25	0.83 to 1.89	1.96	0.68 to 5.61
Duration				
E+P use†				
No HRT use	Ref		Ref	
1-9 years	1.23	0.84 to 1.80	1.36	0.45 to 4.07
≥ 10 years	1.27	0.83 to 1.94	2.36	0.72 to 7.71
P for Trend‡	0.22		0.17	
E use§				
No HRT use	Ref		Ref	
1-9 years	1.06	0.63 to 1.79	2.41	0.81 to 7.16
≥ 10 years	0.91	0.54 to 1.53	1.83	0.68 to 4.94
P for trend‡	0.73		0.22	

Abbreviations: NSCLC, non–small-cell lung cancer; SCLC, small-cell lung cancer; HRT, hormone replacement therapy; Ref, reference; HR, hazard ratio; E, unopposed estrogen; E+P, estrogen plus progestin.

*Adjusted for age, pack-years, pack-years squared, years smoked, personal history of cancer, family history of lung cancer, chronic obstructive pulmonary disease, body mass index (categorical, including missing as a category), age at menopause (categorical, including missing as a category), hysterectomy type, and nonwhite race/ethnicity.

†Years of E+P use alone. Reference group is subjects who never used any form of HRT. Users of E only are excluded from the analysis.

‡*P* for trend analyses by continuous categories.

§Years of E use alone. Reference group is subjects who never used any form of HRT. Users of E+P only are excluded from the analysis.

Table 4. Hazard Ratios for the Association of Hormone Replacement Therapy Use With Incident Lung Cancer Stratified by Stage at Diagnosis

	Local Stage (n = 73)		Advanced Stage* (n = 271)	
HRT Variable	HR	95% CI†	HR	95% CI†
HRT status				
Never user	Ref		Ref	
Former user	1.05	0.49 to 2.26	1.22	0.85 to 1.74
Current user	1.01	0.50 to 2.06	1.29	0.93 to 1.79
HRT formulation				
No use	Ref		Ref	
E use only	0.70	0.29 to 1.66	1.15	0.78 to 1.69
E+P use only	1.27	0.60 to 2.69	1.52	1.06 to 2.19
Use of both	1.24	0.54 to 2.86	1.22	0.81 to 1.84
Duration				
E+P use‡				
No HRT use	Ref		Ref	
1-9 years	1.13	0.53 to 2.44	1.31	0.90 to 1.90
≥ 10 years	1.29	0.57 to 2.91	1.52	1.02 to 2.28
P for trend§	.54		.03	
E use‖				
No HRT use	Ref		Ref	
1-9 years	0.61	0.20 to 1.89	1.31	0.81 to 2.11
≥ 10 years	0.53	0.18 to 1.55	0.97	0.61 to 1.54
P for Trend§	.26		.93	

Abbreviations: HRT, hormone replacement therapy; HR, hazard ratio; Ref, reference; E, unopposed estrogen; E+P, estrogen plus progestin.

*Regional, advanced, or unknown stage.

†Adjusted for age, pack-years, pack-years squared, years smoked, personal history of cancer, family history of lung cancer, chronic obstructive pulmonary disease, body mass index (categorical, including missing as a category), age at menopause (categorical, including missing as a category), hysterectomy type, and nonwhite race/ethnicity.

‡Years of E+P use alone. Reference group is subjects who never used any form of HRT. Users of E only are excluded from the analysis.

§*P* for trend analyses by continuous categories.

‖Years of E use alone. Reference group is subjects who never used any form of HRT. Users of E+P only are excluded from the analysis.

1.99).[11] The Heart and Estrogen/Progestin Replacement Study (HERS) found a nonsignificantly increased risk of lung cancer for women randomly assigned to conjugated E+P (HR = 1.39; 95% CI, 0.84 to 2.28).[25]

Recent Women's Health Initiative analyses found that subjects randomly assigned to E+P had more lung cancer deaths than those taking placebo.[26,27] A retrospective study also found decreased survival among HRT users with lung cancer.[28] SEER collects mortality data, but we did not analyze lung cancer mortality because we do not have information on HRT use after diagnosis. However, to explore a possible explanation for the effect of HRT on lung cancer mortality, we analyzed the association of HRT use with stage at diagnosis and found an increased risk of advanced stages at diagnosis with E+P, consistent with the Women's Health Initiative results on lung cancer mortality.[26,27] Although the mechanisms underlying this association are unknown, E+P may lead to more aggressive disease, may mask early symptoms, and/or users may be less likely to seek or receive medical care in a timely fashion.

The mechanisms that contribute to the association between exogenous hormone therapy and lung cancer risk are complex, with likely genetic and environment interactions.[6,40] Estrogen and progesterone receptors are found in NSCLC tumors[41,42] and the quantity of estrogen receptors is associated with decreased recurrence-free survival.[42] Estradiol promotes growth in NSCLC cell lines that is blocked by antiestrogens.[43] Similarly, a mouse model showed that estradiol increased the proliferative index of cells that had been initiated by expression of oncogenic Kras and concurrent deletion of Tp53.[44] A combination of an estrogen antagonist and epidermal growth factor receptor tyrosine kinase inhibitor decreased tumor volume more than either drug alone in vivo in xenograft models[41,45] and in vitro.[46] Evidence for a protective association of HRT has been shown. Low levels of insulin-like growth factor 1 are associated with reduced risk of lung cancer,[47] and HRT has been shown to decrease insulin-like growth factor 1 levels.[14] Finally, a recent study found several associations between single nucleotide polymorphisms in genes involved with estrogen metabolic pathways and an increased risk of lung cancer.[48]

Our study has several strengths. We used a large, prospective, population-based cohort study design. We were able to analyze the duration of HRT use in a dose-response manner over a long period of time that is likely necessary for biologic plausibility. We controlled for the strong confounding effect of tobacco and examined multiple other variables that affect the risk of incident lung cancer. Finally, the SEER database is complete and accurate, so there is minimal risk of outcome misclassification.

Our results are similar to those observed in the randomized, placebo-controlled HERS trial,[25] but there are potential limitations of our study. First, residual confounding may be a factor. We could not adjust for environmental tobacco or occupational exposures that increase lung cancer risk. However, we did adjust for several smoking variables and did not find evidence of confounding by indication from processes such as oophorectomy for which HRT is commonly taken. Second, the measurement of long-term use of HRT is based on subject recall and was not measured repeatedly. The VITAL questionnaire was validated for long-term use of supplements,[49] suggesting our measure of HRT is reasonably accurate. We expect that exposure misclassification would have attenuated our results in this prospective study. Generalizability may be limited because only 24% of respondents returned the initial survey, but it is unlikely that selection bias could have affected our results because in a prospective design, women cannot participate jointly based on exposure and future (unknown) disease status.

Lung cancer is the second most common malignancy among women and causes more deaths than breast cancer.[1] Our results indicate that the use of E+P is associated with an increased risk of incident lung cancer and advanced stages at diagnosis in a duration-response manner. These findings represent an important contribution to current evidence against HRT use, which may be useful for counseling women about their risk of developing lung cancer, as well as prompting further study about the biologic mechanisms underlying this association.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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REFERENCES

1. Ries LAG MD, Krapcho M, Mariotto A, et al: SEER Cancer Statistics Review, 1975-2004, based on November 2007 SEER data submission, posted to the SEER web site. Bethesda, MD, National Cancer Institute, 2008 http://seer.cancer.gov/csr/1975_2005/

2. Anonymous: The Health Consequences of Smoking: A Report of the Surgeon General. Washington, DC, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, 2004. CDC Publication No. 7829. http://www.cdc.gov/tobacco/sgr/sgr_2004/index.htm

3. Gray J, Mao JT, Szabo E, et al: Lung Cancer Chemoprevention: ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition). Chest 132:56S-68S, 2007

4. Centers for Disease Control and Prevention: Cigarette smoking among adults: United States, 2007. MMWR Morb Mortal Wkly Rep 57:1221-1226, 2008

5. Peto R, Darby S, Deo H, et al: Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. BMJ 321:323-329, 2000

6. Belani CP, Marts S, Schiller J, et al: Women and lung cancer: Epidemiology, tumor biology, and emerging trends in clinical research. Lung Cancer 55:15-23, 2007

7. Thomas L, Doyle LA, Edelman MJ: Lung cancer in women: Emerging differences in epidemiology, biology, and therapy. Chest 128:370-381, 2005

8. Kreuzer M, Gerken M, Heinrich J, et al: Hormonal factors and risk of lung cancer among women? Int J Epidemiol 32:263-271, 2003

9. Rodriguez C, Spencer Feigelson H, Deka A, et al: Postmenopausal hormone therapy and lung cancer risk in the Cancer Prevention Study II nutrition cohort. Cancer Epidemiol Biomarkers Prev 17:655-660, 2008

10. Olsson H, Bladstrom A, Ingvar C: Are smoking-associated cancers prevented or postponed in women using hormone replacement therapy? Obstet Gynecol 102:565-570, 2003

11. Kabat GC, Miller AB, Rohan TE: Reproductive and hormonal factors and risk of lung cancer in women: A prospective cohort study. Int J Cancer 120:2214-2220, 2007

12. Adami HO, Persson I, Hoover R, et al: Risk of cancer in women receiving hormone replacement therapy. Int J Cancer 44:833-839, 1989

13. Taioli E, Wynder EL: Re: Endocrine factors and adenocarcinoma of the lung in women. J Natl Cancer Inst 86:869-870, 1994

14. Schabath MB, Wu X, Vassilopoulou-Sellin R, et al: Hormone replacement therapy and lung cancer risk: A case-control analysis. Clin Cancer Res 10:113-123, 2004

15. Elliott AM, Hannaford PC: Use of exogenous hormones by women and lung cancer: Evidence from the Royal College of General Practitioners' Oral Contraception Study. Contraception 73:331-335, 2006

16. Blackman JA, Coogan PF, Rosenberg L, et al: Estrogen replacement therapy and risk of lung cancer. Pharmacoepidemiol Drug Saf 11:561-567, 2002

17. Liu Y, Inoue M, Sobue T, et al: Reproductive factors, hormone use and the risk of lung cancer among middle-aged never-smoking Japanese women: A large-scale population-based cohort study. Int J Cancer 117:662-666, 2005

18. Mahabir S, Spitz MR, Barrera SL, et al: Dietary boron and hormone replacement therapy as risk factors for lung cancer in women. Am J Epidemiol 167:1070-1080, 2008

19. Chen KY, Hsiao CF, Chang GC, et al: Hormone replacement therapy and lung cancer risk in Chinese. Cancer 110:1768-1775, 2007

20. Schwartz AG, Wenzlaff AS, Prysak GM, et al: Reproductive factors, hormone use, estrogen receptor expression and risk of non small-cell lung cancer in women. J Clin Oncol 25:5785-5792, 2007

21. Ramnath N, Menezes RJ, Loewen G, et al: Hormone replacement therapy as a risk factor for non-small cell lung cancer: Results of a case-control study. Oncology 73:305-310, 2007

22. Omenn GS, Goodman GE, Thornquist MD, et al: Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med 334:1150-1155, 1996

23. Anonymous: The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers: The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. N Engl J Med 330:1029-1035, 1994

24. Rossouw JE, Anderson GL, Prentice RL, et al: Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. JAMA 288:321-333, 2002

25. Hulley S, Furberg C, Barrett-Connor E, et al: Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study Follow-up (HERS II). JAMA 288:58-66, 2002

26. Heiss G, Wallace R, Anderson GL, et al: Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. JAMA 299:1036-1045, 2008

27. Chlebowski RT, Schwartz AG, Wakelee H, et al: Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): A post-hoc analysis of a randomised controlled trial. Lancet 374:1243-1251, 2009

28. Ganti AK, Sahmoun AE, Panwalkar AW, et al: Hormone replacement therapy is associated with decreased survival in women with lung cancer. J Clin Oncol 24:59-63, 2006

29. Prentice RL: Methodologic challenges in chronic disease population research. Biostatistics 2:365-381, 2001

30. White E, Patterson RE, Kristal AR, et al: VITamins And Lifestyle cohort study: Study design and characteristics of supplement users. Am J Epidemiol 159:83-93, 2004

31. Zippin C, Lum D, Hankey BF: Completeness of hospital cancer case reporting from the SEER

Program of the National Cancer Institute. Cancer 76:2343-2350, 1995

32. Field RW, Smith BJ, Platz CE, et al: Lung cancer histologic type in the surveillance, epidemiology, and end results registry versus independent review. J Natl Cancer Inst 96:1105-1107, 2004

33. Patterson RE, Kristal AR, Tinker LF, et al: Measurement characteristics of the Women's Health Initiative food frequency questionnaire. Ann Epidemiol 9:178-187, 1999

34. Kristal AR, Patterson RE, Neuhouser ML, et al: Olestra Postmarketing Surveillance Study: Design and baseline results from the sentinel site. J Am Diet Assoc 98:1290-1296, 1998

35. Kristal AR, Feng Z, Coates RJ, et al: Associations of race/ethnicity, education, and dietary intervention with the validity and reliability of a food frequency questionnaire: The Women's Health Trial Feasibility Study in Minority Populations. Am J Epidemiol 146:856-869, 1997

36. Lin DY, Wei LJ: The robust inference for the Cox proportional hazards model. J Am Stat Assoc 84:1074-1078, 1989

37. Slatore CG, Littman AJ, Au DH, et al: Long-term use of supplemental multivitamins, vitamin C, vitamin E, and folate does not reduce the risk of lung cancer. Am J Respir Crit Care Med 177:524-530, 2008

38. Hersh AL, Stefanick ML, Stafford RS: National use of postmenopausal hormone therapy: Annual trends and response to recent evidence. JAMA 291:47-53, 2004

39. U.S. Preventive Services Task Force: Hormone therapy to prevent chronic conditions in postmenopausal women: Recommendations from the U.S. Preventive Services Task Force. Ann Intern Med 142:I-59, 2005

40. Chen GG, Zeng Q, Tse GM: Estrogen and its receptors in cancer. Med Res Rev 28:954-974, 2008

41. Márquez-Garbán DC, Chen HW, Fishbein MC, et al: Estrogen receptor signaling pathways in human non-small cell lung cancer. Steroids 72:135-143, 2007

42. Raso MG, Behrens C, Herynk MH, et al: Immunohistochemical expression of estrogen and progesterone receptors identifies a subset of NSCLCs and correlates with EGFR mutation. Clin Cancer Res 15:5359-5368, 2009

43. Stabile LP, Davis ALG, Gubish CT, et al: Human non-small cell lung tumors and cells derived from normal lung express both estrogen receptor alpha and beta and show biological responses to estrogen. Cancer Res 62:2141-2150, 2002

44. Hammoud Z, Tan B, Badve S, et al: Estrogen promotes tumor progression in a genetically defined mouse model of lung adenocarcinoma. Endocr Relat Cancer 15:475-483, 2008

45. Stabile LP, Lyker JS, Gubish CT, et al: Combined targeting of the estrogen receptor and the epidermal growth factor receptor in non-small cell lung cancer shows enhanced antiproliferative effects. Cancer Res 65:1459-1470, 2005

46. Pietras RJ, Marquez DC, Chen HW, et al: Estrogen and growth factor receptor interactions in human breast and non-small cell lung cancer cells. Steroids 70:372-381, 2005

47. Yu H, Spitz MR, Mistry J, et al: Plasma levels of insulin-like growth factor-i and lung cancer risk: A case-control analysis. J Natl Cancer Inst 91:151-156, 1999

48. Cote ML, Yoo W, Wenzlaff AS, et al: Tobacco and estrogen metabolic polymorphisms and risk of non-small cell lung cancer in women. Carcinogenesis 30:626-635, 2009

49. Satia-Abouta J, Patterson RE, King IB, et al: Reliability and validity of self-report of vitamin and mineral supplement use in the vitamins and lifestyle study. Am J Epidemiol 157:944-954, 2003

