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Unopposed Estrogen and Estrogen Plus Progestin Menopausal Hormone Therapy and Lung Cancer Risk in the NIH-AARP Diet and Health Study Cohort

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Abstract

Purpose—Previous studies have reported that lung cancer risk may either be decreased, increased or unaffected by prior use of menopausal hormone therapy (MHT).

Methods—To examine this issue further, we examined relationships among 118,008 women, ages 50–71 years who were recruited during 1995–1996 for the NIH-AARP Diet and Health Study and in whom 2,097 incident lung carcinomas were identified during follow-up through 2006. Multivariable Cox proportional hazards models estimated relative risks (RR) and 95% confidence intervals (CIs) associated with various measures of self-reported MHT use.

Results—We found no evidence that either estrogen therapy (ET)-only or estrogen plus progestin therapy (EPT) use was substantially related to subsequent lung cancer risk (respective RRs and 95% CIs for ever use = 0.97, 0.86–1.09 and 1.03, 0.90–1.17). There were no significant variations according to currency or duration of use of either formulation, nor was there evidence that risks varied within subgroups defined by cigarette smoking or body size. The absence of effect was seen for nearly all lung cancer subtypes, with the exception of an increased risk of undifferentiated/large cell cancers associated with long-term ET-only use (P_{trend}=0.02), a relationship not observed among EPT users.

Conclusions—Our results failed to support any substantial alterations in lung cancer risk associated with use of either unopposed estrogen or estrogen plus progestin MHT, even when detailed exposure measures and other risk predictors were considered.

Keywords

lung cancer; menopausal hormone therapy; risk; histology

Introduction

Although cigarette smoking has been established as a strong risk factor for lung cancer, the fact that overall in the U.S. about 15% of cases occur among non-smokers has prompted a

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focus on other etiologic exposures. That higher rates of cancers among non-smokers develop among women than men has stimulated attention regarding a variety of hormonally-related risk factors (1). Although the majority of studies do not support a role for most hormonally-related factors (2), a number of studies have demonstrated that menopausal hormone therapy (MHT) may be associated with a decrease in the risk of subsequent lung cancer (3–9).

Several theories have been postulated to support the possible anticarcinogenic activity of MHT. It is well recognized that normal as well as cancerous lung tissues express estrogen receptors, particularly non-small cell lung carcinomas (NSCLCs), which differentially express estrogen receptor (ER) β (10). These receptors, as well as vitamin D receptors, can bind with exogenous hormones, displacing tobacco-related carcinogens and leading to reduced proliferation (6).

Despite the plausibility of the association, a number of studies have failed to note a significant relationship of MHT on lung cancer risk (11–14). Notable among these studies has been the Women's Health Initiative clinical trial, which found no substantial effect of estrogen therapy (ET) on lung cancer incidence (13). However, in the estrogen plus therapy (EPT) arm of the trial, there was a small, but non-significant increase in the incidence of NSCLCs, as well as a significant increase in the risk of death from lung cancers (15). These findings were more consistent with other studies that have observed that menopausal hormones may increase lung risk among certain users, including long-term users (16), users of EPT (17) or older women (18), or predispose to certain tumor subtypes, such as adenocarcinomas (19;20).

Resolution of the inconsistent findings of the role of MHT in lung cancer risk is complex given that many lung cancer risk factors are strongly correlated with use and could have confounding effects. These include cigarette smoking, social class, body mass index (BMI), and type and age at menopause. Although most of the previous studies have attempted to control for these factors, residual confounding is possible. Relationships may also vary by histologic subgroups, which have been shown to differentially relate to a number of risk factors.

We previously assessed the role of a number of reproductive and hormonal factors on the risk of lung cancer in the large NIH-AARP Diet and Health Cohort Study (2). Although we did not find any substantial relationship of MHT to risk, we utilized information from the baseline questionnaire, which did not allow us to distinguish risk according to type of therapy prescribed. Using information from a subsequently administered questionnaire, we were able to assess risk in relation to more detailed parameters of use, including recency of use, duration, regimen and formulation. Given that estrogens and progestins may have differential effects on cancer risk, this additional information provided an enhanced opportunity to understand relationships of MHT to lung cancer risk overall and within specific histologic subgroups.

Methods

Study Population

The NIH-AARP Diet and Health Study Cohort was established in 1995–1996 when a questionnaire requesting information on demographic characteristics, dietary intake, and health-related behaviors was sent to 3.5 million AARP members (21). Recipients of the questionnaire included members aged 50–71 years who resided in one of six U.S. states (CA, FL, LA, NJ, NC, and PA) or two metropolitan areas (Atlanta, GA, and Detroit, MI). A total of 617,119 persons (17.6%) returned the questionnaire, with 566,402 (16.2%) satisfactorily completing it. In 1996–1997, a second questionnaire was sent to collect

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additional information on diet, physical activity, and use of menopausal hormones, with a 59.5% response rate (n=337,074). After excluding participants who died (n=1,619), moved out of the study area before their second questionnaires were received and scanned (n=547), had proxies complete their baseline (n=6,959) or second (3,424) questionnaires, withdrew from the study (n=2), or were male (n=188,116), 136,407 potentially eligible women remained. The Special Studies Institutional Review Board of the National Cancer Institute approved this study.

Exposure Ascertainment

As described elsewhere (2), the baseline questionnaire asked whether women were currently taking “replacement hormones”, and, if so, for how many years. The second questionnaire collected detailed data for both estrogen and progestin on ever use, dates of first and last use, total duration of use, regimen, usual dose, and name of the pill that was used for the longest period of time. Subjects were only asked about individual years of usage up to 10 years, with responses for longer term users aggregated as one category. We used reported ages at first and last use to estimate longer term usage for selective analyses.

We considered women who reported taking both estrogen and progestin pills to have used only estrogen plus progestin if the reported dates of first use were within 90 days of each other or if reported durations of use were identical. Sequential regimens included estrogen plus progestin use for fewer than 15 days per cycle, whereas continuous estrogen plus progestin regimens included use for more than 15 days per cycles, including use every day.

Cohort Follow-up

Cohort members were followed annually for address changes and vital status. Address changes were identified through linkage to the U.S. Postal Service’s (USPS) National Change of Address database, USPS updates received with undeliverable mail, use of other address change update services, and participants’ notifications. Vital status was updated through linkage to the Social Security Administration Death Master File and verified by the National Death Index (NDI).

Incident Cancers

Based on annually updated residence information and using first and last name, address, sex, date of birth, and social security number obtained from the baseline questionnaire, incident cases of lung cancers were identified by probabilistic linkage to the cancer registries in the eight states from which study subjects were derived as well as two states to which subjects tended to move (Texas and Arizona). All suspected matches underwent review to reject the potential matches that were unlikely to be true (an estimated 4%), and uncertain matches underwent final manual review. An earlier validation study that compared registry findings with self-reports and medical records estimated that linkage validly identified approximately 90% of all incident cancers among study participants (22).

Dates of diagnosis and tumor characteristics were obtained from the cancer registries. Using histologic codes from the International Classification of Diseases for Oncology (ICD-O-3) (23), all primary incident cancers of the bronchus and lung (ICD 34.0–34.9) were considered for the present analysis. Lung cancer cases included small cell carcinomas (8041, 8042, 8043, 8044, 8045), adenocarcinomas (8140, 8250, 8251, 8252, 8253, 8254, 8255, 8260, 8310, 8323, 8480, 8481, 8490, 8550), squamous cell carcinomas (8050, 8070, 8071, 8072, 8073, 8074, 8075, 8083), undifferentiated/large cell carcinomas (8012, 8020, 8022, 8031, 8032), non-small cell carcinomas not otherwise specified (NOS) (8046), and other carcinomas NOS (8010, 8011, 8033, 8560).

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Analytic Population

We excluded 9,036 women who reported a personal history of cancer other than non-melanoma skin cancer on either questionnaire, 7 women who died or were diagnosed with cancer on the first day of follow-up, 4,006 without information on cigarette smoking, 89 without information on MHT use, 963 with extreme values for caloric intake (defined as more than two interquartile ranges above the 75th or below the 25th percentile of log transformed intake), 4,298 premenopausal women. Analyses therefore focused on 118,008 women.

Most women who use ET have had a hysterectomy. However, older women with intact uteri likely had opportunities to take ET before added progestins became routine. We therefore analyzed ET associations in the entire cohort as well as in the 49,703 women with hysterectomy at baseline who never used hormone or who only used ET. We limited the assessment of EPT to the 67,581 women with intact uteri at baseline and further restricted analyses to women who never used hormones or only used EPT.

Study entry and follow-up began at the date at which the second questionnaire was received and scanned, and continued until December 31, 2006 or the earliest of the following: participant diagnosed with lung cancer, moved out of the registry catchment area, or died from any cause. During follow-up in our study, a total of 2,097 of the eligible study participants developed lung carcinomas. Lung cancers that could not be defined as carcinomas (n=281) were censored at diagnosis, including 132 with only death certificate diagnoses, 69 neoplasms NOS, 37 carcinoid neoplasms, 32 neuroendocrine tumors, 7 sarcomas, 2 *in situ* squamous cancers and 2 mesotheliomas.

Statistical Analysis

We used Cox proportional hazards regression (using SAS 9.1.3 software, SAS Institute, Inc., Cary, NC), with age as the time scale and ties handled by complete enumeration (24), to estimate the relative risks (RR) and 95% confidence intervals (CI) of developing lung cancer. Tests of the proportional hazards assumptions for exposures and other variables included in statistical models revealed no departures.

We initially evaluated potential confounding by all identified risk factors but ultimately chose a parsimonious combination of variables that were associated with both exposure and outcome and changed any of the parameter estimates of interest by more than 10% compared with estimates from models adjusted only for age at entry. Our statistical models adjusted for age at entry, race/ethnicity, body mass index, history of emphysema, smoking status and number of cigarettes per day, age at menarche, and type and age at menopause (including oophorectomy status). Finer adjustment for smoking (including by six levels of number of cigarettes per day, four levels of time since quitting, and a combination of the two variables) and adjustment for additional risk factors (cigar and pipe smoking, years of education, alcohol consumption, levels of physical activity, intake of fruits, vegetables, red meat or processed meat, and total daily energy intake) had minimal effects on risks.

Tests for linear trends across the known exposure categories were calculated by treating these categorical variables as ordinal variables. We used a likelihood ratio test, comparing models with and without the interaction terms, to separately examine effect modification of MHT by cigarette smoking (never, former, current smoker) and BMI (<25, 25–29, ≥30 kg/m^2). In addition, we examined whether the relationship between MHT use and lung cancer incidence differed by tumor histology (small cell, adenocarcinoma, squamous cell, non-small cell NOS, undifferentiated/large cell). Probability values of <0.05 were considered statistically significant. All tests of statistical significance were two-tailed.

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Results

Characteristics of the Cohort

The 118,008 women contributed 1,100,627 person-years. The median ages at entry for lung cancer cases and non-diseased subjects were 64.6 and 62.8 years, respectively. The mean durations of follow-up (and upper range) were 5.4 years (10.1) for those who developed lung cancer (n=2,097) and 9.4 (10.2) for those who did not.

Most women in the cohort were white and in their 60s when they completed the baseline questionnaire. Lung cancer risk was positively associated with cigarette smoking, alcohol consumption, higher levels of consumption of red meat and processed meat, and a history of having been diagnosed with emphysema. Inverse relations of risk were observed with being married, years of education, adult BMI, higher levels of physical activity, and higher intakes of fruits and vegetables.

Hormone Usage Patterns

A total of 38.5% of the study subjects had never used hormones, while 28.6% were ET-only users and 28.2% EPT users. Smaller proportions of the cohort used other combinations of therapy, e.g., ET only followed by EPT (4.6%) (Table 1).

Compared with non-users of hormones, women who had used hormones were more likely to be younger, white, married, former smokers and thin (BMI <25 kg/m^2). ET users were more likely to have had a surgical menopause, especially at young ages. EPT users were more likely than ET users to be younger, be college graduates, and report excellent or very good health at baseline.

Unopposed Estrogen Therapy (ET)

Among all women, there was no substantial evidence that ever use of ET was related to lung cancer risk (RR=0.97, 95% CI 0.86–1.09) (Table 2). Further, there was no evidence that risk was affected by longer durations of use (including the extended duration variable estimated from ages at first and last use which allowed assessment of risks beyond 20 or more years, data not shown). Similar risks were seen for current and former users, and there was no evidence of any trends of risk with duration of use among current users or with time since last use among former users. Analyses restricted to women with a hysterectomy at baseline confirmed an absence of associations with ET, although most estimates were slightly lower than those observed among all women.

Estrogen Plus Progestin Therapy (EPT)

Among women with intact uteri, EPT use was not associated with lung cancer risk (RR=1.03, 0.90–1.17) (Table 3). Current users were at a slightly lower risk (0.97) than former users (1.19), but the difference was not statistically significant. There was no evidence of any trends of risk with duration of use, even when examined among current users. Risk also did not vary by whether progestins were used sequentially or continuously, or by progestin dose or days progestins were used.

Modifications of Relationships by Other Factors

We saw no significant heterogeneity according to smoking status (never, former, current smokers) for either ET or EPT (Table 4). Risks also did not vary significantly according to BMI (<25, 25–29, 30+) (data not shown).

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Histologic Variation

Although there was no significant heterogeneity in risks associated with ET or EPT use according to histology (Table 5), we did observe a significant trend in risk (P=0.02) of undifferentiated/large cell tumors with years of ET use, with the risk associated with 10 or more years of use being significantly elevated (RR=1.96, 1.07–3.60, based on 29 cases).

We were able to further stratify the adenocarcinomas according to smoking status, as there were a number of such tumors that developed among never smokers. However, we observed no evidence of differential effects of MHT use according to smoking status within this restricted histologic subgroup (data not shown).

Discussion

Although a number of previous studies have suggested that users of MHT may be at a reduced risk of lung cancer, we saw no evidence for this in our large prospective study. Our analyses evaluated risk in relation to detailed parameters of use, and allowed us to distinguish relationships of ET from EPT. In addition, given the large numbers of study subjects, we were able to evaluate effect modification by other important lung cancer predictors (e.g., cigarette smoking, body mass index) and to assess variation in risks by tumor histology.

Discrepancies between our results and previous studies that have found reduced risks of lung cancer associated with MHT may reflect that a number of these studies were case-control investigations (3;4;6;8;9), raising questions regarding the possibility of selective inclusion of study subjects and recall biases. The use of hospital or clinic controls in several studies (6;8) is of particular concern given that access to the medical care system can affect drug usage patterns (25) and may have resulted in especially high rates of usage of hormones.

In contrast to case-control studies, cohort studies have generally not observed reduced risks associated with MHT use. The notable exception is the large Cancer Prevention II Study, which did note a significant reduction in risk for current use of either ET or EPT (RR=0.76, 95% CI 0.62–0.92), but saw no evidence of a dose-response relation with years of use (7). The remaining cohort studies have either noted no relationship of MHT to risk (26) or possibly some elevated risk among certain subgroups of users (11;17;19;27–29), as discussed in detail in a recent meta-analysis (30). However, results from some of these studies must be cautiously interpreted given small numbers or an inability to completely control for potential confounders.

Complete control for confounding requires special attention given that a number of lung cancer risk factors tend to be highly correlated with the probability of MHT exposure. Of major concern is the possibility of residual confounding by cigarette smoking, which might have explained hormone associations in other investigations, especially among selected subgroups of users. Although we did not have information on duration of cigarette smoking, residual confounding would seem unlikely given that we did not observe much variation in MHT rates according to smoking status, nor did we observe much change in risks after finely adjusting for number of cigarettes or interval since smoking cessation. Other factors, such as being thin or having early menopause, which are generally associated with both high rates of MHT use and lung cancer risk (2;29), also did not appear to confound hormone associations.

In contrast to our previous investigation within the NIH-AARP study (2), a strength of the current analysis was that we were able to focus on differences between use of ET versus EPT. This was of interest given recent findings supporting a role of progesterone receptor

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expression in both the etiology and prognosis of lung cancers (31). However, we found no substantial differences according to the formulations prescribed. Further, among EPT users, we noted no variation in risks according to whether the progestins were prescribed sequentially or continuously, nor did we observe an impact of dose of the progestin reportedly prescribed. Our results showing no particular distinction for combination therapy are in accord with most previous studies (8), although are at variance with some studies that have shown either significant (17), or non-significant increases in all lung cancers (11) or NSCLCs (15).

Although we did not observe any overall associations with hormone use, it was of interest to assess relationships within groups defined by smoking as well as body mass given that these factors are both strongly related to lung cancer risk and have been shown to affect measures of endogenous hormones (32). Several previous studies have found variations according to smoking, including pronounced reductions in risk associated with MHT use among either former (6) or current (8) smokers. In the latter study, it was hypothesized that this could reflect that MHT binds more readily to estrogen receptors than polycyclic aromatic hydrocarbons, limiting the potential for carcinogenic activity of smoking constituents. However, the study found the greatest reductions in risk for the lightest smokers, requiring cautious interpretation of the results.

Interactions with cigarette smoking are also difficult to interpret in some of the studies because this exposure can also affect the histology of the tumors. In nonsmokers, adenocarcinomas are higher in women than men (33) and these tumors tend to more frequently possess estrogen receptors or estrogen binding sites as compared with other tumor types (34). Although one previous study found MHT use to be associated with a reduction only in the risk of NSCLCs and not small cell carcinomas (8), we did not observe significant variations in risks according to histology. We did observe an increased risk of undifferentiated/large cell cancers associated with extended durations of ET-only use, although this was based on a relatively small number of cases and could have reflected the play of chance.

A somewhat less appreciated risk factor for lung cancer than cigarette smoking is body mass, which has been shown in many studies, including this one (29), to be inversely associated with risk. Thin women have been shown to have lower levels of endogenous hormones (32), most likely explaining higher exogenous hormone-associated risks among thin women for other cancers, including those arising in the endometrium and breast (35;36). Several studies have suggested that hormone effects for lung cancer may also vary by body mass index (6;8), although in the opposite direction than other hormonally-related cancers—namely greater inverse associations among thin women. We, however, observed no significant heterogeneity in the relationships of either ET or EPT use to risk according to body mass.

In summary, in this largest study to date, we saw little evidence that MHT significantly affected the subsequent development of lung carcinomas. Importantly, we were able to assess effects of different types of MHT preparations and formulations, carefully control for a number of possible confounders, evaluate numerous potential effect modifiers, and assess relationships for different types of tumors. Thus, although there has been accumulating interest in the relationship of hormonal factors to lung cancer risk, our results do not support that MHT has any substantial impact. This is consistent with accumulating evidence against an important role for most other factors that may operate through hormonal mechanisms, including most reproductive factors (36). The one factor, however, for which there is emerging data for a potential adverse effect on lung cancer risk is early menopause (2;11;37–40), although seemingly not due to increased menopausal hormone usage.

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Supplementary Material

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Abbreviations used

NCI	National Cancer Institute
AARP	American Association of Retired Persons
MHT	menopausal hormone therapy
RR	relative risk
CI	confidence interval
ET	estrogen therapy
PT	progestin therapy
EPT	estrogen plus progestin therapy
VEGF	vascular endothelial growth factor
NSCLC	non-small cell lung cancer
NOS	not otherwise specified
BMI	body mass index

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Table 1

Distribution of Study Subjects by MHT Use and Selected Factors, NIH-AARP Diet and Percent of Study Subjects by Hormone Use Categories

	None	ET-Only	EPT	Other/Unknown
Study subjects	45,443	33,798	33,339	5,428
Age at study entry				
<57	14.6	18.7	23.8	19.4
57–60	17.1	19.9	26.1	21.4
61–64	24.4	24.3	24.0	24.0
65–68	31.7	26.8	20.0	26.1
≥69	12.3	10.2	6.1	9.2
Race, %				
Caucasian	89.4	91.8	93.7	88.7
Black	6.3	4.5	2.4	6.6
Other/unknown	4.3	3.8	3.9	4.7
Married, %	38.5	46.9	49.7	45.5
College graduate, %	26.8	27.8	41.7	28.0
Cigarette smoking, status and number of cigarettes/day, %				
Never	46.5	46.0	44.4	45.9
Former, ≤20	25.9	28.0	30.0	27.9
Former, >20	11.6	12.7	14.4	12.9
Current, ≤20	11.8	9.6	7.9	9.8
Current, >20	4.2	3.9	3.3	3.5
Menopausal type and age at menopause at baseline, years				
Natural Menopause, <45	9.7	3.0	6.7	5.6
Natural Menopause, 45–49	21.9	5.8	19.1	12.1
Natural Menopause 50–54	38.3	8.4	38.0	20.1
Natural Menopause, ≥55	7.7	1.6	9.8	5.3
Bilaterial oophorectomy, <40	2.6	14.1	3.0	9.1
Bilaterial oophorectomy, 40–44	1.9	11.0	2.8	6.7
Bilaterial oophorectomy, 45–49	1.8	11.7	3.4	6.8
Bilaterial oophorectomy, ≥50	1.1	6.5	3.0	5.0
Hysterectomy/intact ovaries, <40	5.0	14.8	2.9	9.9
Hysterectomy/intact ovaries, 40–44	3.0	8.1	1.5	5.8
Hysterectomy/intact ovaries, 45–49	1.8	4.9	1.1	3.4
Hysterectomy/intact ovaries, ≥50	0.8	1.7	0.7	1.4
Other/unknown	2.9	7.4	1.8	5.9
Surgical other, unknown	1.5	1.1	6.1	2.9
BMI at baseline				
<25	38.7	43.5	52.3	43.0
25–29	31.8	32.9	29.8	32.4
≥30	25.4	20.7	15.4	20.9

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	None	ET-Only	EPT	Other/Unknown
Self-reported health status at baseline				
Excellent	17.0	14.9	21.7	15.2
Very Good	34.8	34.7	38.4	34.3
Good	34.5	36.5	30.4	34.7
Fair/Poor	12.6	12.9	8.7	14.7

Column percentages; totals do not add to 100% due to missing values.

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Table 2

Associations Between ET-only Use and Lung Cancer Risk, NIH-AARP Diet and Health Study Cohort

ET-only Use	All Women (n=118,008)					Women with Hysterectomy (n=49,703)				
	No. cancers	Person-Years	RR	95% CI		No. cancers	Person-Years	RR	95% CI	
Ever use										
No	883	421,418	1.00	reference		219	92,838	1.00	reference	
Yes	621	314,682	0.97	0.86	1.09	524	267,549	0.93	0.79	1.09
p-value for trend					*0.33*					*0.29*
Recency of use										
Former	201	85,924	0.98	0.83	1.14	135	55,709	0.99	0.79	1.23
Current	412	225,260	0.96	0.84	1.10	383	209,497	0.91	0.77	1.08
p-value for trend					*0.3*					*0.19*
Duration of use (y)										
<5	208	103,227	0.98	0.84	1.15	143	68,451	1.01	0.82	1.25
5–9	92	52,136	1.03	0.82	1.29	78	47,222	0.96	0.74	1.25
≥10	313	156,278	0.93	0.80	1.08	296	149,709	0.88	0.73	1.05
p-value for trend					*0.22*					*0.09*
Duration of use among current users (y)										
<5	64	44,515	0.87	0.67	1.13	54	35,030	0.91	0.67	1.23
5–9	64	39,319	1.09	0.83	1.41	59	37,488	1.01	0.75	1.35
≥10	284	140,762	0.97	0.83	1.13	270	136,378	0.90	0.75	1.08
p-value for trend					*0.66*					*0.22*
Time since last use among former users (y)										
<5	38	21,048	0.98	0.71	1.36	27	14,684	0.95	0.63	1.42
5–9	22	11,548	0.91	0.60	1.40	14	7,258	0.86	0.50	1.48
≥10	79	32,191	0.86	0.68	1.09	53	20,600	0.88	0.65	1.19
p-value for trend					*0.13*					*0.24*

RR adjusted for age, race, age at menarche, menopausal type and age, BMI, emphysema diagnosis, cigarette smoking status and number of cigarettes/day, and other hormone therapy formulations (EPT only, ET then EPT, PT then EPT, ET, ET then PT, PT then ET, EPT then PT, EPT then EPT unknown, other combinations, unknown regimens).

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Table 3

Associations between EPT Use Among Women with Intact Uteri and Lung Cancer Risk, NIH-AARP Diet and Health Study Cohort

EPT Use	Women with intact uteri (n=67,581)			
	No. cancers	Person-Years	RR	95% CI
Ever use				
No	656	325,087	1.00	reference
Yes	381	239,314	1.03	0.90 1.17
p-value for trend				*0.61*
Recency of use				
Former	109	54,805	1.19	0.97 1.45
Current	266	181,086	0.97	0.84 1.13
p-value for trend				*0.92*
Duration of use (y)				
<5	165	101,313	1.11	0.93 1.32
5–9	85	70,094	0.83	0.66 1.05
≥10	123	62,473	1.11	0.91 1.35
p-value for trend				*0.65*
Duration of use among current users (y)				
<5	88	61,576	1.07	0.85 1.34
5–9	69	61,105	0.79	0.61 1.01
≥10	109	57,425	1.06	0.86 1.30
p-value for trend				*0.85*
Time since last use among former users (y)				
<5	32	15,987	1.37	0.96 1.96
5–9	10	5,196	1.11	0.59 2.07
≥10	4	2,238	0.83	0.31 2.21
p-value for trend				*0.52*
Regimen of use				
Sequential (<15d)	112	80,231	0.93	0.76 1.15
Continuous	232	140,617	1.06	0.91 1.24
p-value for trend				*0.51*

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EPT Use	Women with intact uteri (n=67,581)				
Progestin dose (mg)					
<1	9	8,793	0.69	0.36	1.34
2.5	179	113,871	1.02	0.86	1.20
5	51	32,776	1.05	0.79	1.41
10	34	26,551	0.87	0.61	1.23
p-value for trend				*0.86*	
Days Progestin					
<10	33	18,113	1.17	0.82	1.67
10–14	48	41,187	0.85	0.63	1.14
15–19	6	3,453	1.33	0.59	2.97
20–25	24	18,298	0.81	0.54	1.22
Daily	146	87,341	1.13	0.94	1.36
p-value for trend				*0.35*	

RR adjusted for age, race, age at menarche, menopausal type and age, BMI, emphysema diagnosis, cigarette smoking status and number of cigarettes/day, and other hormone therapy formulations.

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Table 4

Associations between ET-only and EPT Use and Lung Cancer Risk by Smoking Status, NIH-AARP Diet and Health Study Cohort

	Never Smoker (n= 53,953)			**Former Smoker (n= 47,800)**			**Current Smoker (n= 16,255)**		
	No. cancers	**RR**	**95% CI**	**No. cancers**	**RR**	**95% CI**	**No. cancers**	**RR**	**95% CI**
ET only use - All women									
No	72	1.00	reference	354	1.00	reference	457	1.00	reference
Yes	49	0.90	0.59 1.38	280	0.95	0.79 1.14	292	1.00	0.85 1.18
p-value for trend			*0.66*			*0.44*			*0.76*
Receny of use									
Former	14	0.97	0.54 1.75	76	0.84	0.65 1.09	111	1.10	0.89 1.37
Current	35	0.88	0.55 1.41	199	0.99	0.81 1.22	178	0.95	0.78 1.16
p-value for trend			*0.63*			*0.77*			*0.43*
Duration of use (y)									
<5	9	0.55	0.27 1.11	94	1.03	0.81 1.30	105	1.01	0.81 1.26
5–9	8	1.00	0.46 2.17	38	0.89	0.63 1.26	46	1.20	0.88 1.65
≥10	30	1.07	0.65 1.79	146	0.90	0.72 1.13	137	0.95	0.76 1.18
p-value for trend			*0.58*			*0.22*			*0.53*
	Never Smoker (n= 30,473)			Former Smoker (n=27,518)			Current Smoker (n= 9,590)		
	No. cancers	RR	95% CI	No. cancers	RR	95% CI	No. cancers	RR	95% CI
EPT use - Women with intact uteri									
No	54	1.00	reference	263	1.00	reference	339	1.00	reference
Yes	28	0.85	0.53 1.38	180	0.98	0.81 1.20	173	1.14	0.94 1.38
p-value for trend			*0.56*			*0.87*			*0.17*
Recency of use									
Former	6	0.78	0.34 1.83	54	1.20	0.89 1.61	49	1.27	0.94 1.72
Current	21	0.85	0.50 1.45	124	0.91	0.73 1.14	121	1.09	0.88 1.35
p-value for trend			*0.54*			*0.54*			*0.34*
Duration of use (y)									

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	Never Smoker (n= 53,953)				Former Smoker (n= 47,800)				Current Smoker (n= 16,255)			
	No. cancers	**RR**	**95% CI**		**No. cancers**	**RR**	**95% CI**		**No. cancers**	**RR**	**95% CI**	
<5	10	0.75	0.37	1.49	78	1.07	0.83	1.39	77	1.25	0.97	1.61
5–9	6	0.65	0.27	1.55	39	0.77	0.55	1.09	40	0.97	0.69	1.35
≥10	11	1.17	0.60	2.30	59	1.06	0.79	1.42	53	1.18	0.88	1.58
p-value for trend			*0.98*				*0.83*				*0.28*	

RR adjusted for age, race, age at menarche, menopausal type and age, BMI, emphysema diagnosis, cigarette smoking status and number of cigarettes/day, and other hormone therapy formulations.

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Table 5

Associations between ET-only and EPT Use and Lung Cancer Risk by Histology, NIH-AARP Diet and Health Study Cohort

				Non-Small Cell Carcinomas											
	Small Cell (n= 357)			**Adenocarcinoma (n= 928)**			**Squamous Cell (n= 279)**			**Non-small cell, NOS (n= 248)**			**Undifferentiated/ Large cell (n= 109)**		
Hormone Therapy	RR	95% CI		RR	95% CI		RR	95% CI		RR	95% CI		RR	95% CI	
ET only use - All women															
No	1.00	reference		1.00	reference		1.00	reference		1.00	reference		1.00	reference	
Yes	0.97	0.73	1.29	0.90	0.75	1.08	0.88	0.64	1.22	1.09	0.77	1.53	1.50	0.90	2.50
Recency of use															
Former	0.91	0.62	1.35	0.91	0.71	1.17	0.80	0.52	1.25	1.13	0.72	1.77	1.66	0.89	3.09
Current	1.02	0.74	1.41	0.90	0.73	1.10	0.89	0.61	1.28	1.09	0.74	1.63	1.46	0.81	2.62
Duration of use (y)															
<5	1.09	0.76	1.55	0.83	0.64	1.07	1.04	0.70	1.55	1.17	0.75	1.81	1.14	0.56	2.32
5–9	1.19	0.71	1.98	0.88	0.62	1.26	0.95	0.51	1.75	0.99	0.49	1.99	1.19	0.41	3.45
≥10	0.83	0.57	1.20	0.96	0.77	1.19	0.71	0.47	1.08	1.08	0.70	1.67	1.96	1.07	3.60
				Non-Small Cell Carcinomas											
	Small Cell (n= 203)			Adenocarcinoma (n= 500)			Squamous Cell (n= 157)			Non-small cell, NOS (n= 147)			Undifferentiated/ Large cell (n= 58)		
Hormone Therapy	RR	95% CI		RR	95% CI		RR	95% CI		RR	95% CI		RR	95% CI	
EPT use - Women with intact uteri															
No	1.00	reference		1.00	reference		1.00	reference		1.00	reference		1.00	reference	
Yes	0.91	0.66	1.25	1.05	0.86	1.28	0.88	0.60	1.27	1.26	0.87	1.83	1.19	0.66	2.16
Recency of Use															
Former	0.99	0.58	1.67	1.27	0.94	1.72	1.05	0.59	1.88	1.26	0.70	2.29	1.87	0.85	4.14
Current	0.90	0.63	1.29	0.97	0.78	1.21	0.81	0.52	1.24	1.29	0.86	1.94	0.88	0.43	1.82
Duration of use (y)															
<5	0.88	0.56	1.39	1.10	0.84	1.42	0.83	0.49	1.42	1.56	0.98	2.47	1.45	0.69	3.05
5–9	0.85	0.49	1.46	0.82	0.58	1.16	0.69	0.34	1.38	1.03	0.54	1.96	0.87	0.30	2.53

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				Non-Small Cell Carcinomas										
	Small Cell (n= 357)			Adenocarcinoma (n= 928)			Squamous Cell (n= 279)			Non-small cell, NOS (n= 248)			Undifferentiated/ Large cell (n= 109)		
≥10	0.97	0.59	1.59	1.19	0.89	1.59	1.12	0.66	1.90	1.18	0.66	2.10	1.24	0.50	3.05

RR adjusted for age, race, age at menarche, menopausal type and age, BMI, emphysema diagnosis, cigarette status and number of cigarettes/day, and other hormone therapy formulations.