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MENOPAUSAL HORMONE THERAPY DOES NOT INFLUENCE LUNG CANCER RISK: RESULTS FROM THE CALIFORNIA TEACHERS STUDY

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Abstract

Background—Results from studies examining the association between hormone therapy (HT) and lung cancer risk disagree.

Methods—We examined the associations between HT use and lung cancer risk among 60,592 postmenopausal women enrolled in the prospective California Teachers Study cohort. Between 1995 and 2007, 727 women were diagnosed with lung cancer. Multivariable Cox proportional hazards regression models were fit using age as the time metric.

Results—No measure of HT use was associated with lung cancer risk (all p-values for trend≥0.4). In addition, no variations in risk by smoking status (never, ever, former, current), type of HT (E-alone, E+P use), type of menopause, or lung cancer histology were observed.

Conclusions—Our findings do not support an association between HT and lung cancer.

Impact—This large-scale, prospective study, which capitalizes on the detailed hormone use, smoking history, and type of menopause information available within this unique cohort, was unable to find any association between intake of HT and lung cancer risk.

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Introduction

Cigarette smoking, the leading cause of lung cancer, is responsible for 80–90% of lung malignancies(1). Nevertheless, lung cancers develop among lifetime never smokers highlighting the need to investigate other factors that may modify lung cancer risk(2). Lung cancer pathology, risk factors and prognosis differ by sex, prompting researchers to investigate hormonal and reproductive factors(3). The association between hormone therapy (HT) and lung cancer has been investigated; however, the results have differed across studies(4–5). We examined HT use in relation to lung cancer risk among women in the California Teacher Study (CTS) capitalizing on detailed information on HT use (including formulation, duration and timing), smoking history, and type of menopause.

Methods

Study Population

The CTS cohort, established in 1995–1996, consists of 133,479 active and retired female teachers and administrators(6). CTS participants residing in California are followed annually for cancer diagnosis and death. The questionnaire participants completed at baseline covered a wide range of issues related to cancer risk and women's health, including recent and past HT use, menopausal status, and cigarette smoking. For estrogen (E), questions were asked about Premarin® as well as other estrogens and information was collected on mode of administration, dose if Premarin® was used, ages at first and last use, and duration of use. For progestins (P), participants were asked to report the type of progestin used, ages at first and last use, years of use, days per month of use, and dose. A five-category smoking variable was created based on baseline smoking status and median pack-years (never, former light, former heavy, current light, and current heavy).

Women were sequentially excluded from the analytic cohort if not a California resident at baseline (n=8,867), the medical history portion of the questionnaire was incomplete (n=662), participant reported a prior diagnosis of lung cancer at baseline (n=215), or participant limited her participation to breast cancer research (n=18). Additionally, we excluded premenopausal women (n=47,976), women with indeterminate menopausal status (n=4,957), women missing information on smoking (n=2,924), and women with incomplete HT histories (n=7,268). Of 60,592 eligible postmenopausal women, 727 were diagnosed with lung cancer a month or more after joining the cohort and before December 31, 2007.

Statistical Analyses

Relative risks (RR) and 95% confidence intervals (CI) for lung cancer associated with HT use were estimated using multivariable Cox proportional hazards regression with age (days) used as the timescale. Models were age stratified (years) and adjusted for race/ethnicity, smoking status/pack-years, type of menopause, and body mass index (BMI, kg/m^2). Follow-up time began on the date the baseline questionnaire was completed and ended on the date of lung cancer diagnosis, death, move out of California, or December 31, 2007, whichever occurred first.

Results

A majority (74.5%) of eligible postmenopausal women had used HT; 16.0% were former and 58.5% were current users of either E-alone or E+P therapy at baseline (Table 1). In the multivariable model, use of any HT was not associated with lung cancer risk (RR, 0.95, 95% CI, 0.80–1.13) (Table 2). Neither former HT use nor recent HT use (i.e., current use at baseline) was associated with risk (RR, 0.98, 95% CI, 0.79–1.21; RR, 0.94, 95% CI, 0.78–1.13; respectively). No association was observed for duration of use (*p-trend*=0.46) or years

since quitting HT use (≤5 years: RR, 1.11, 95% CI, 0.80–1.55; >5 years: RR, 0.92, 95% CI, 0.71–1.18). Further, we observed no variations in risk by smoking status (never, ever, former, current) (Table 2), type of HT (E-alone, E+P use), type of menopause, or lung cancer histology (data not shown).

Discussion

We observed no associations between HT-use and lung cancer risk in this large study of postmenopausal women with up to eleven years of follow-up. One explanation for the lack of effect may be the overwhelming magnitude of the association between smoking and lung cancer masking smaller associations with other exposures, such as HT. However, if this were true, we would expect to observe significant HT-use lung cancer associations among never smokers, and we did not.

A recent meta-analysis of eleven studies did not support an association between HT-use and lung cancer risk(5). In contrast, Greiser et al. reported a significant increased risk of lung cancer among never-smokers(4). However, in that study, significant associations were only found when smokers and non-smokers, various hormone regimens, or histological subtypes, respectively, were pooled(4). Furthermore, combined risk estimates from meta-analyses are difficult to interpret, in part due to study heterogeneity, and should be interpreted with considerable caution.

One limitation of our study is that residual confounding from smoking may exist. However, a major strength was our use of a five-category smoking variable that combined smoking status and median pack-years to control for both smoking status and smoking intensity.

Overall, our findings do not support an association between HT and lung cancer.

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Table 1

Age-adjusted baseline characteristics among 60,592 postmenopausal California Teachers Study participants by baseline status of hormone therapy (HT) use

Characteristic	N (total)	HT use at baseline (estrogen alone or estrogen plus progestin)		
		Never HT user	Former HT user	Recent HT user
No. participants	60,592	15,405	9,716	35,471
No. invasive lung cancer cases	727	216	147	364
Mean age at baseline ± SD		65.6 ± 11.4	67.5 ± 10.5	59.7 ± 9.4
Race/ethnicity (%)[1]				
White	54,275	24.5	16.1	59.4
Other[2]	5,789	33.1	15.8	51.1
Menopausal status (%)[3]				
Perimenopausal	2,184	41.9	9.7	48.5
Postmenopausal, Natural menopause	31,748	34.1	17.5	48.4
Postmenopausal, Other	21,945	11.6	13.7	74.7
Smoking status (%)[3]				
Never smoker	37,138	25.2	14.5	60.3
Former smoker	19,901	20.9	15.1	64.0
Current smoker	3,553	29.7	15.4	54.9
Mean pack-years ± SD		20.7 ± 21.2	20.3 ± 20.8	16.8 ± 18.0
Mean body mass index, kg/m^2 ± SD		25.7 ± 5.5	25.5 ± 5.1	24.9 ± 4.8
Body mass index, kg/m^2 (%)[3]				
<25	32,679	21.6	13.7	64.7
25–29	14,116	23.9	15.7	60.5
≥30	10,563	28.8	16.0	55.2

[1] Percents for race/ethnicity are crude percents

[2] The Other category for race/ethnicity includes: Hispanic, Native American, Asian/Pacific Islander, Mixed and Unknown

[3] Percents are age-standardized by 5-year age categories based on the age distribution of the analytic cohort; missing and unknown not shown

Table 2

Multivariable-adjusted relative risks (RR) and 95% confidence intervals (CI) for the association between hormone therapy (HT) use and incident invasive lung cancer among 60,592 postmenopausal California Teachers Study participants

	Total		Never Smokers		Ever Smokers	
HT Use	**N Total/Cases**	**Adjusted[1,2] RR (95% CI)**	**N Total/Cases**	**Adjusted[1,3] RR (95% CI)**	**N Total/Cases**	**Adjusted[1,4] RR (95% CI)**
Ever HT Use						
Never HT user	15,405/216	1.00	9,912/55	1.00	5,493/161	1.00
Ever HT user (Former and Recent HT users)	45,187/511	0.95(0.80–1.13)	27,226/129	1.06(0.76–1.50)	17,961/382	0.93(0.77–1.14)
Former or Recent HT Use						
Never HT user	15,405/216	1.00	9,912/55	1.00	5,493/161	1.00
Former E alone or E+P user	9,716/147	0.98(0.79–1.21)	5,871/43	1.21(0.80–1.82)	3,845/104	0.93(0.72–1.19)
Recent E alone or E+P user	35,471/364	0.94(0.78–1.13)	21,355/86	0.98(0.67–1.43)	14,116/278	0.94(0.76–1.16)
Type of HT Used						
Never HT user	15,405/216	1.00	9,912/55	1.00	5,493/161	1.00
Former E alone or E+P user	9,569/147	0.99(0.79–1.22)	5,871/43	1.20(0.79–1.81)	3,845/104	0.94(0.73–1.21)
Recent E alone therapy	15,663/188	0.97(0.77–1.23)	9,730/43	0.92(0.57–1.49)	5,933/145	1.00(0.76–1.31)
Recent E+P combined therapy	19,808/177	0.92(0.74–1.13)	11,625/43	1.02(0.66–1.59)	8,183/133	0.89(0.70–1.14)
Duration of HT Use						
Never HT user	15,405/216	1.00	9,912/55	1.00	5,493/161	1.00
Ever HT user, ≤ 5 years duration	19,670/167	0.93(0.76–1.15)	12,205/48	1.08(0.72–1.63)	7,465/119	0.91(0.71–1.16)
Ever HT user, 6–15 years duration	13,866/151	0.92(0.74–1.14)	8,081/42	1.18(0.76–1.82)	5,785/109	0.85(0.66–1.10)
Ever HT user, ≥ 15 years duration	9,122/151	0.95(0.75–1.20)	5,399/30	0.88(0.54–1.45)	3,723/121	0.98(0.76–1.28)
	P-trend	*0.71*		*0.92*		*0.71*
Duration of HT Use						
Never HT user	15,405/216	1.00	9,912/55	1.00	5,493/161	1.00
Former HT user						
≤ 5 years duration	6,278/97	1.04(0.82–1.33)	3,802/31	1.50(0.96–2.35)	2,476/66	0.93(0.70–1.25)
6–15 years duration	2,038/31	0.89(0.60–1.31)	1,224/8	0.93(0.42–2.09)	814/23	0.87(0.55–1.36)
≥ 15 years duration	920/13	0.78(0.44–1.39)	530/2	0.53(0.13–2.21)	390/11	0.89(0.47–1.68)
	P-trend	*0.46*		*0.99*		*0.48*
Recent HT user						
≤ 5 years duration	13,392/70	0.81(0.60–1.09)	8,403/17	0.69(0.37–1.30)	4,989/53	0.86(0.61–1.20)
6–15 years duration	11,828/120/	0.92(0.72–1.17)	6,857/34	1.25(0.77–2.02)	4,971/86	0.84(0.63–1.12)
≥ 15 years duration	8,202138	0.92(0.72–1.17)	4,869/28	0.93 (0.55–1.57)	3,333/110	0.93(0.70–1.23)
	P-trend	*0.56*		*0.60*		*0.40*
Years Since Last HT Use for Former Users						
Never HT user	15,405/216	1.00	9,912/55	1.00	5,493/161	1.00
Former HT user, ≤ 5 years since last use	3,746/47	1.11(0.80–1.55)	2,176/10	1.11(0.55–2.25)	1,570/37	1.12(0.77–1.63)

HT Use	Total		Never Smokers		Ever Smokers	
	N Total/Cases	Adjusted[1,2] RR (95% CI)	N Total/Cases	Adjusted[1,3] RR (95% CI)	N Total/Cases	Adjusted[1,4] RR (95% CI)
Former HT user, > 5 years since last use	5,927/100	0.92(0.71–1.18)	3,659/33	1.32(0.83–2.11)	2,268/67	0.81(0.60–1.10)

[1] Stratified by age at baseline

[2] Adjusted for race, smoking status/pack-years combination (never, former light, former heavy, current light, current heavy), type of menopause and BMI

[3] Adjusted for race, type of menopause and BMI

[4] Adjusted for race, smoking status/pack-years combination (former light, former heavy, current light, current heavy), type of menopause and BMI