Postmenopausal Hormone Therapy and Lung Cancer Risk in the Cancer Prevention Study II Nutrition Cohort

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Abstract

Background: **Studies of postmenopausal hormone therapy and lung cancer incidence have reported positive, negative, and null associations. Most of these studies, however, have had limited ability to control rigorously for cigarette smoking or to examine risk separately by smoking status.**

Methods: **We examined the association between postmenopausal hormone therapy and lung cancer incidence by smoking status among 72,772 women in the Cancer Prevention Study II Nutrition Cohort. Proportional hazards modeling was used to calculate rate ratios (RR).**

Results: **During follow-up from 1992 to 2003, we identified 659 cases of incident lung cancer. Current use of any postmenopausal hormone therapy was significantly associated with decreased risk of incident lung cancer [multivariate RR, 0.76; 95% confidence interval (95% CI), 0.62-0.92]. Similar risk estimates were observed for unopposed estrogen use (RR, 0.76; 95% CI, 0.60-0.94) and for estrogen plus progestin (RR, 0.76; 95% CI, 0.57-1.01). Risk associated with current use of postmenopausal hormone therapy was decreased among never smokers (RR, 0.56; 95% CI, 0.33-0.95) as well as current smokers (RR, 0.76; 95% CI, 0.55-1.05) and former smokers (RR, 0.76; 95% CI, 0.58-0.99). Former hormone use was not associated with lung cancer. No trend with duration of hormone use was detected.**

Conclusion: **These results support the hypothesis that postmenopausal hormone therapy is associated with reduced risk of lung cancer, although the absence of a dose-response relationship weakens the evidence for causality.** (Cancer Epidemiol Biomarkers Prev 2008; 17(3):655–60)

Introduction

Lung cancer is the leading cause of cancer mortality in women in the United States (1). Mortality rates have at best leveled off among women while decreasing among men; thus, the male/female ratio has changed from 2.4 in the period 1989 to 1991 (2) to 1.9 in 1998 to 2002 (1). Although the gender difference in trends represents mainly differences in tobacco use by sex, lung cancer has somewhat different clinical and biological characteristics in women than in men. Tumors in women are predominantly adenocarcinoma (3), incidence rates are slightly higher at younger ages (4), and 5-year relative survival is greater in women than in men (5, 6). In addition, estrogen and progesterone receptor expression has been identified in normal and tumor lung cells, suggesting a role for sex hormones on lung cancer (7-9).

Studies on postmenopausal hormone therapy and lung cancer incidence have produced mixed results; two studies found increased risk (10, 11), although the association was not statistically significant in one of them (11); some found a significant inverse relation (12, 13) or nonsignificant inverse relation (14, 15), and others found no association (16-20). No association was found in the Women's Health Initiative (WHI; refs. 18, 21), the only randomized trial to report on this association, although the WHI trial had limited statistical power to examine this relationship. Cigarette smoking is by far the most important risk factor for lung cancer in U.S. women; however, only five (10, 12, 13, 17, 19) studies controlled in detail for duration and intensity of smoking among current smokers and time since cessation among former smokers. Because of the strength of the association between tobacco smoking and lung cancer and the possibility of residual confounding due to differences in smoking intensity, duration, and age at cessation, the potential relationship between postmenopausal hormone therapy and lung cancer can best be examined in studies that can assess the association separately in lifelong nonsmokers. Six studies have examined this association among never smokers; two found a nonstatistically significant lower risk of lung cancer among postmenopausal hormone users (12, 13), one reported increased risk only among postmenopausal hormone users with induced menopause (11), whereas no association was seen in the other three (10, 15, 17). Importantly, only two studies (11, 13) were adequately powered to examine the association separately in lifelong nonsmokers.

Although postmenopausal hormone therapy use decreased substantially following the July 2002 publication of results from the WHI (18, 21), its use remains highly prevalent (22, 23). It is of both etiologic and public health interest to clarify its association, if any, with lung cancer.

Received 10/10/07; revised 12/13/07; accepted 12/19/07.

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doi:10.1158/1055-9965.EPI-07-2683

The Cancer Prevention Study II (CPS-II) Nutrition Cohort is sufficiently large to examine the risk of lung cancer associated with postmenopausal hormone therapy separately among current, former, and never smokers. We examined the association between postmenopausal hormone use and lung cancer incidence in time-dependent analyses that controlled closely for smoking behavior among 72,772 postmenopausal U.S. women.

Subjects and Methods

Study Cohort and Follow-up. Women in this study were selected from among the 97,786 female participants in the CPS-II Nutrition Cohort (hereafter referred to as the Nutrition Cohort), a prospective study of cancer incidence and mortality among 184,190 U.S. men and women (24). The Nutrition Cohort is a subgroup of the ~1.2 million participants in the CPS-II, a prospective mortality study established by the American Cancer Society in 1982 (25). Members of the CPS-II mortality cohort who resided in 21 states with population-based state cancer registries and were ages 50 to 74 years in 1992 were invited to participate in the Nutrition Cohort by completing a mailed questionnaire. The recruitment and characteristics of Nutrition Cohort participants are described in detail elsewhere (24). All aspects of the CPS-II Nutrition Cohort study are approved by the Emory University Institutional Review Board.

At enrollment in 1992, participants completed a self-administered mailed questionnaire that included demographic, medical, anthropometric, behavioral, environmental, occupational, and dietary factors. Follow-up questionnaires were sent to cohort members in 1997, 1999, 2001, and 2003 to update exposure information and to ascertain newly diagnosed cancers. The response rate among living participants for each of the follow-up questionnaires (after multiple mailings) was at least 89%. For the present study, the follow-up period ended on June 30, 2003.

We excluded from this analysis 3,190 women who were lost to follow-up (that is, were not known to be dead at the time of the first follow-up questionnaire in 1997 but failed to return the 1997 follow-up questionnaire or any subsequent questionnaire). We also excluded women who reported any prevalent cancer (except nonmelanoma skin cancer) at baseline (n = 12,096), those whose self-report of lung cancer on the 1997 questionnaire could not be verified, or had conflicting information on year of lung cancer diagnosis (n = 17). The study population was restricted to postmenopausal women; therefore, we excluded women who were premenopausal or had unknown menopausal status or unknown age at menopause (n = 2,067). A total of 2,922 women were entered into the analysis as they became postmenopausal during follow-up. We excluded women with missing information on postmenopausal hormone use or unknown type (n = 4,598) and those who reported use of oral progesterone alone or vaginal cream alone at baseline (n = 1,918). We also excluded women who reported use of combination therapy in spite of having had a previous hysterectomy (n = 772). In addition, because smoking is by far the strongest risk factor for lung cancer, we excluded women with incomplete or conflicting smoking information (n = 356). After exclusions, the analytic cohort consisted of 72,772 women. Women who developed cancer (other than lung cancer or nonmelanoma skin cancer) during the follow-up, those whose self-report of lung cancer on the 1999 or subsequent questionnaires could not be verified (n = 94), and cohort members with missing hormone data on the follow-up questionnaires were censored at the time of their data report (n = 22,553).

A total of 659 primary lung cancer cases were diagnosed in the interval between enrollment in 1992 and June 30, 2003. Some lung cancer cases (n = 287) were initially identified through a self-report of lung cancer on questionnaire and subsequently verified by medical records (n = 175) or by linkage with state cancer registries (n = 112). A previous study linking cohort members to state cancer registries indicated that the ability of our respondents to report a past diagnosis of cancer is high (sensitivity, 0.93; ref. 17). Another 352 cases were ascertained as deaths due to lung cancer through linkage with National Death Index (26) among participants who did not report lung cancer on any of the previous questionnaires. Additional clinical information was obtained for 243 of these deaths through subsequent linkage with state cancer registries. Finally, 20 women who did not self-report lung cancer on any of the questionnaires were identified as having lung cancer during the process of verifying a different cancer through linkage with a state cancer registry.

Information on tumor histology was available for 71% (n = 470) of the lung cancer cases; of these, 55% (n = 258) were adenocarcinomas, 30% (n = 142) were squamous or large cell carcinomas, and 15% (n = 70) were small cell carcinomas.

Ascertainment of Postmenopausal Hormone Therapy. Postmenopausal hormone therapy was assessed at enrollment in 1992 and on each follow-up questionnaire. In addition, because all Nutrition Cohort participants were historically participants in the larger CPS-II cohort (25), information on prospectively collected hormone use was also available from the 1982 CPS-II questionnaire. The 1992 baseline questionnaire and the 1997 follow-up questionnaires included questions on current and past postmenopausal hormone therapy use as well as type and duration of use. Later follow-up questionnaires (1999 and 2001) included only questions regarding type of hormone use in the last 2 years. At study entry, women were classified into separate exclusive categories as never, current, or former users of each type-specific hormone therapy [unopposed estrogen (ET) or estrogen plus progestin (E + P)]. Information from the 1982 CPS-II questionnaire was used to define never and former users. Never users at baseline include women who reported never use of any type of hormone replacement therapy in 1982 and 1992. Because we did not ask type of hormone therapy on the 1982 CPS-II questionnaire, women who reported never hormone use in 1992 but marked hormone use in the 1982 CPS-II questionnaire were considered former ET users. Women who reported current use of E + P in 1992 and hormone use in 1982 were classified as E + P users, although some of them may have use ET before 1982.

Ascertainment of Smoking Status. Smoking history was assessed at enrollment in 1992 and on each follow-up

questionnaire as well as from 1982 when participants were enrolled in the CPS-II Nutrition Cohort. Based on information from 1982 and 1992, women were classified as current, former, or never smokers (those who reported having smoked <100 cigarettes in their entire life on the 1992 survey and also reported never smoking on the 1982 questionnaire). Information was also available on number of cigarettes per day, years of smoking, and years since smoking cessation.

Because 89.1% of participants in the CPS-II Nutrition Cohort were married to men who were also in the CPS-II Nutrition Cohort, smoking information from 62,706 spouses was linked to women included in the analytic cohort to provide a measure of secondhand smoke exposure from spousal smoking.

Statistical Analysis. Cox proportional hazards modeling was used to examine the association between hormone use and incident lung cancer while adjusting for confounding factors. Hormone use was calculated as a time-dependent variable based on information reported in the 1992, 1997, 1999, and 2001 questionnaires. Never users were defined as women who reported never use of any type of postmenopausal hormone therapy up to each of the time intervals included in the model.

All Cox models were stratified on exact year of age at enrollment. Potential confounders included in the multivariate models were education, smoking status, spousal tobacco exposure, body mass index, age at menopause, oral contraceptive use, physical activity, and whole-fruit and total β-carotene consumption. All covariates with the exception of physical activity (metabolic equivalents in quartiles), whole-fruit consumption (in quartiles), and β-carotene consumption (in quintiles) were modeled using the categories shown in Table 1.

Race, age at menarche, parity, hysterectomy, intake of vegetables, multivitamin intake, and vitamin E supplement use were also examined as potential confounders but were not included in the final models because such adjustment had negligible effects on the results (data not shown).

Trend tests for duration of postmenopausal hormone therapy use were conducted by assigning the median years of use to each category of hormone therapy.

Information on tumor histology was used to assess separately the association between postmenopausal hormone therapy (ET and E + P combined) and adenocarcinoma, large cell carcinoma, squamous carcinoma, and small cell carcinoma. We also evaluated whether the association between postmenopausal hormone therapy and lung cancer was modified by the potential confounders described above or by attained age. Effect modification was assessed using the likelihood ratio test to compare models with and without interaction terms.

Results

Fifty-five percent (n = 40,013) of women in the study population were current or former users of postmenopausal hormone therapy at study entry (Table 1). Among current hormone users, 62% (n = 15,200) were current ET users and 38% (n = 9,224) used E + P. Eight percent (n = 748) of women classified as current E + P users reported hormone use in 1982. Compared with never users, current users were more likely to be more educated and thinner, to be former smokers, and have stopped smoking for a longer time. They were also considerably younger than never or former users. Compared with never users, age at menopause (natural or artificial) was earlier for women who were former or current users of ET and later for E + P users.

An inverse association was observed between current users of ET and E + P and risk of lung cancer (Table 2) and risk estimates were similar for both hormone regimens. Compared with women who reported no use of any type of postmenopausal hormone therapy, risk of lung cancer was 24% lower among current ET and current E + P users [fully adjusted rate ratio (RR), 0.76; 95% confidence interval (95% CI), 0.60-0.94 for ET users; RR, 0.76; 95% CI, 0.57-1.01 for E + P users; Table 2]. Therefore, we combined both types of hormone regimens in all the following analyses. Current use of any postmenopausal hormone therapy was associated with 24% lower risk of lung cancer compared with never users (RR, 0.76; 95% CI, 0.62-0.92). Former use of any postmenopausal hormone therapy was not associated with risk of lung cancer (RR, 0.89; 95% CI, 0.73-1.07).

To further examine whether the observed inverse association between postmenopausal hormone therapy and risk of lung cancer could be due to residual confounding by smoking, we did stratified analysis to assess lung cancer risk among women who were lifelong never smokers (Table 3). Smoking did not significantly (P = 0.98) modify the association between postmenopausal hormone use and risk of lung cancer, although the inverse association appeared strongest among lifelong never smokers than current or former smokers. Current use of postmenopausal hormones was associated with decreased risk of lung cancer among never smokers (RR, 0.56; 95% CI, 0.33-0.95), current smokers (RR, 0.76; 95% CI, 0.55-1.05), and former smokers (RR, 0.76; 95% CI, 0.58-0.99).

No dose-response relationship between duration of postmenopausal hormone use and lung cancer was observed among current users (P_{trend} = 0.54). Risk estimates were similar among women who used postmenopausal hormones <5 years (RR, 0.79; 95% CI, 0.57-1.09 based on 43 cases), 5 to <10 years (RR, 0.78; 95% CI, 0.55-1.10 based on 38 cases), or >10 years (RR, 0.75; 95% CI, 0.59-0.94 based on 106 cases).

Current use of postmenopausal hormones was associated with a statistically significantly decreased risk of adenocarcinoma (RR, 0.63; 95% CI, 0.46-0.86 based on 71 lung cancer cases) and small cell carcinoma (RR, 0.42; 95% CI, 0.22-0.83 based on 12 lung cancer cases). No significant association was seen for squamous carcinomas (RR, 1.20; 95% CI, 0.75-1.92 based on 36 lung cancer cases) and large cell carcinomas (RR, 1.14; 95% CI, 0.47-2.74 based on 11 lung cancer cases).

We found no statistically significant interactions between current postmenopausal hormone use and any covariates included in the multivariate model.

Discussion

This large prospective study supports the observation that postmenopausal hormone therapy is associated with

Table 1. Age-adjusted percentages and medians of selected baseline characteristics by categories of postmenopausal hormone therapy status at study entry (CPS-II Nutrition Cohort, 1992-2003)

	Hormone replacement therapy status in 1992				
	Never user	Current ET user	Former ET user	Current E + P user	Former E + P user
n	32,759	15,200	11,988	9,224	3,601
Age group*					
<55	7.9	12.3	3.6	14.6	10.1
55-64	53	56.2	35.3	69.1	61.5
65-74	36.7	30.2	57	15.9	27.4
≥75	2.3	1.4	4.1	0.4	1
Education level					
Less than high school	6.7	4.5	7	2	4
High school graduate	35.8	29.7	35.3	19.5	26.8
Some college	28.8	34.8	33	32.4	33
College graduate/graduate school	28.7	30.9	24.8	46	36.2
Smoking status					
Never	57.8	55.6	54.2	51.2	51
Current					
<20 cigarettes/d, <35 y smoking	2.2	1.7	2.2	1.9	1.8
<20 cigarettes/d, ≥35 y smoking	3.3	2	2.9	2.2	2.6
≥20 cigarettes/d, <35 y smoking	1.3	0.9	1.5	0.8	1.2
≥20 cigarettes/d, ≥35 y smoking	2.9	2.1	3.8	1.6	2.1
Former (years since smoking cessation)					
≤5	5.1	5.1	5.7	5.7	5.9
>5-10	4.1	4.4	4.6	4.7	5.2
>10-15	3.6	4.5	4.5	4.6	4.8
>15-20	3.3	3.9	3.9	4.8	4.8
>20-25	4.3	5	4.5	6.3	5
>25	10.9	13.9	11.3	15.3	15
Unknown	1.1	0.9	1	0.8	0.7
Spousal tobacco exposure					
Spouse not in study	14.2	12.9	14.3	13	13.4
Never	26.2	27.2	24.4	29.1	27
Former	52.5	53.9	54.1	51.9	53.2
Current	7.1	6	7.2	6.1	6.5
Body mass index in 1992 (kg/m^2)					
<25.0	49.6	56.5	48.2	67	57
25.0-<30.0	32.2	31.1	33.3	24.9	29.3
≥30.0	18.2	12.4	18.5	8.1	13.7
Age (y) at menopause					
<45	16.1	44.3	37.4	5.6	15.1
45-<50	25.3	26.8	27.4	20.3	23.1
50-<52	22.5	11.9	15.3	24.5	20.4
≥52	36.1	17	20	49.6	41.4
Oral contraceptive use					
Never	68.9	57.1	64.3	50.7	54.9
Ever, <5 y	17	25.2	23	26.3	26
Ever, ≥5 y	14.1	17.7	12.7	23	19.1
Total β-carotene intake (μg/d)					
Median	1,846	1,918	1,865	1,959	1,944
Whole-fruit consumption (servings/wk)					
Median	8	9	9	9	9
Metabolic equivalents (h/wk)					
Median	7.5	8	7.5	8	8

*Age reported at study entry. Percentages were adjusted to the age distribution of the entire population.

lower risk of incident lung cancer. Lower risk of lung cancer was observed for current use of both estrogen only and combined therapy and among never, current, and former smokers. No association was seen in former users of hormone therapy. The association in current users was not related to duration of hormone use.

Our results differ somewhat from the null results reported for lung cancer as a secondary outcome by the WHI (18), a ~5-year-long randomized clinical trial designed primarily to address the effect of postmenopausal hormones therapy on coronary heart disease and breast cancer. However, the WHI included only 104 cases of lung cancer and the risk estimate for lung cancer incidence (RR, 1.04; 95% CI, 0.71-1.53) does not rule out an effect of the size observed in our study. It remains possible that the association observed in our study is due to confounding by unknown or poorly measured factors. The absence of a dose-related reduction in risk with increasing duration of postmenopausal hormone therapy use suggests that our results could be due to confounding rather than a causal effect. However, smoking is the most likely candidate for residual confounding in a study of lung cancer, and the inverse association between hormone use and lung cancer risk was strongest among never smokers. Also, similarly to the relationship between postmenopausal hormone use and risk of breast

Table 2. RR (95% CI) for the association between postmenopausal hormone therapy use and lung cancer incidence (CPS-II Nutrition Cohort, 1992-2003)

	No. cases	Person-years	RR (95% CI)*	RR (95% CI) †
Postmenopausal hormone therapy use				
Never	304	254,847	1.00 (Reference)	1.00 (Reference)
Current ET	123	148,318	0.72 (0.59-0.89)	0.76 (0.60-0.94)
Former ET	125	97,083	0.94 (0.76-1.16)	0.84 (0.68-1.05)
Current P + E	64	90,366	0.69 (0.52-0.91)	0.76 (0.57-1.01)
Former P + E	43	37,070	1.01 (0.73-1.39)	1.03 (0.74-1.42)
Never	304	254,847	1.00 (Reference)	1.00 (Reference)
Current postmenopausal hormone therapy ‡	187	238,684	0.71 (0.59-0.86)	0.76 (0.62-0.92)
Former postmenopausal hormone therapy ‡	168	194,153	0.95 (0.79-1.15)	0.89 (0.73-1.07)

*Adjusted for age at interview.
†Adjusted for age at interview, smoking status, spousal tobacco exposure in 1992, body mass index in 1992, age at menopause, education, weekly servings of fruit, physical activity, total β-carotene intake, and oral contraceptive use.
‡Any postmenopausal hormone use.

cancer (27), the association observed in current but not former hormone users argues against confounding as an explanation.

Most previous observational studies on postmenopausal hormone therapy and risk of lung cancer have been limited by a small number of lung cancer cases (10, 11, 15, 16, 20). Only four studies (12, 13, 17, 19) included >300 lung cancer cases in their analyses. Of those, two reported no association (17, 19) and two reported statistically significant lower risk of lung cancer among postmenopausal hormone users (12, 13). In a large U.S. hospital-based case-control study (13), both estrogen therapy alone [odds ratio (OR), 0.65; 95% CI, 0.47-0.89] and E + P therapy (OR, 0.61; 95% CI, 0.40-0.92) were associated with reduced risk of lung cancer. The association between postmenopausal hormone use and lung cancer, however, was statistically significant among smokers (OR, 0.59; 95% CI, 0.38-0.92) but failed to reach statistical significance among never smokers due to a small number of lung cancer cases (OR, 0.72; 95% CI, 0.37-1.40). Similarly, risk of lung cancer was reduced among women using postmenopausal hormones for more than 6 years (OR, 0.53; 95% CI, 0.37-0.93) in a case-control study in Germany (12), but the association was only statistically significant among smokers (OR, 0.48; 95% CI, 0.27-0.86 smokers; OR, 0.71; 95% CI, 0.37-1.36 nonsmokers).

Biological evidence for a hormone-related etiology of lung cancer is limited. Steroid hormones act as tumor promoters to increase cell proliferation in target organs, such as breast and endometrium (28); however, their role on lung cancer risk and prognosis is unclear. Estrogen and progesterone receptors are expressed in lung tumor cell lines, normal lung cells, and adenocarcinoma, squamous, and small cell carcinoma human lung cancer (7, 8, 29, 30). A role of progesterone in lung carcinogenesis

Table 3. RR (95% CI) for the association between postmenopausal hormone therapy use and lung cancer incidence by smoking status (CPS-II Nutrition Cohort, 1992-2003)

	Postmenopausal hormone therapy use		
	Never	Current postmenopausal hormone therapy*	Former postmenopausal hormone therapy*
All cases			
No. cases	304	187	168
RR (95% CI) †	1.00 (Reference)	0.71 (0.59-0.86)	0.95 (0.79-1.15)
RR (95% CI) ‡	1.00 (Reference)	0.76 (0.62-0.92)	0.89 (0.73-1.07)
Never smokers			
No. cases	45	23	21
RR (95% CI) †	1.00 (Reference)	0.63 (0.38-1.05)	0.89 (0.53-1.50)
RR (95% CI)§	1.00 (Reference)	0.56 (0.33-0.95)	0.84 (0.50-1.43)
Current smokers			
No. cases	128	60	65
RR (95% CI) †	1.00 (Reference)	0.75 (0.55-1.02)	0.93 (0.69-1.26)
RR (95% CI) ‡	1.00 (Reference)	0.76 (0.55-1.05)	0.92 (0.68-1.26)
Former smokers			
No. cases	131	104	82
RR (95% CI) †	1.00 (Reference)	0.80 (0.62-1.04)	0.90 (0.68-1.19)
RR (95% CI) ‡	1.00 (Reference)	0.76 (0.58-0.99)	0.88 (0.66-1.17)

*Any postmenopausal hormone use.
†Adjusted for age at interview.
‡Adjusted for age at interview, smoking status, spousal tobacco exposure in 1992, body mass index in 1992, age at menopause, education, weekly servings of fruit, physical activity, total β-carotene intake, and oral contraceptive use.
§Adjusted for age at interview, spousal tobacco exposure in 1992, body mass index in 1992, age at menopause, education, weekly servings of fruit, physical activity, total β-carotene intake, and oral contraceptive use.

is suggested by results from recent study of non-small cell lung cancer specimens from 228 patients who underwent surgical resection (9). Progesterone receptor-positive non-small cell lung cancer was more frequently detected in women than men and also more frequently in adenocarcinoma subtype lung cancer; in addition, progesterone inhibited proliferation in these progesterone receptor–positive cells and progesterone receptor–positive status was associated with better outcome. Hormone therapy could also inhibit lung carcinogenesis by reducing levels of insulin-like growth factor-I (29, 30), which is a potent mitogen for several cancers, including lung cancer.

Some study limitations may affect our findings. In spite of the large size of the study that allowed us to separately assess the association between hormone use and lung cancer among women who were never smokers, some analyses relied on small numbers of lung cancer. The strength of the study is our historical detailed prospective information on smoking and spousal smoking, which allowed us to control for spousal environmental tobacco exposure in addition to individual smoking intensity, duration, and time since smoking cessation.

In conclusion, results of this study provide support for the hypothesis that postmenopausal hormone therapy is associated with reduced risk of lung cancer risk and suggest that this association may be independent of smoking status. Postmenopausal hormone use has declined considerably since publication of the WHI results in 2002; however, use is still quite common. An estimated 18 million prescriptions for the two most commonly prescribed hormone therapies were written for U.S. women in 2005 alone (23). Given the prevalence of postmenopausal hormone use and the high incidence and mortality of lung cancer, further studies to confirm this hypothesis and to understand the biological mechanisms underlying a protective effect of postmenopausal hormone use on lung cancer are warranted.

References

1. American Cancer Society. Cancer facts and figures 2007. Atlanta: American Cancer Society; 2007.
2. American Cancer Society. Cancer facts and figures 1996. Atlanta: American Cancer Society; 1996.
3. Thun MJ, Lally CA, Flannery JT, Calle EE, Flanders WD, Heath CW. Cigarette smoking and changes in the histopathology of lung cancer. J Natl Cancer Inst 1997;89:1580–6.
4. Radzikowska E, Glaz P, Roszkowski K. Lung cancer in women: age, smoking, histology, performance status, stage, initial treatment and survival: a population-based study of 20,561 cases. Ann Oncol 2002; 13:1087–93.
5. Alexiou C, Onyeaka CV, Beggs D, et al. Do women live longer following lung cancer resection for carcinoma? Eur J Cardiothorac Surg 2002;21:319–25.
6. Visbal AL, Williams BA, Nichols FC III, et al. Gender differences in non-small-cell lung cancer survival: an analysis of 4,618 patients diagnosed between 1997 and 2002. Ann Thorac Surg 2004;78:209–15.
7. Chaudhuri PK, Thomas PA, Walker MJ, Briele HA, Das Gupta TK, Beattie CW. Steroid receptors in human lung cancer cytosols. Cancer Lett 1982;16:327–32.
8. Mollerup S, Jorgensen K, Berge G, Haugen A. Expression of estrogen receptors α and β in human lung tissue and cell lines. Lung cancer 2002;37:153–9.
9. Ishibashi H, Suzuki T, Suzuki S, et al. Progesterone receptor in non-small cell lung cancer—a potent prognostic factor and possible target for endocrine therapy. Cancer Res 2005;65:6450–8.
10. Taioli E, Wynder E. Re: endocrine factors and adenocarcinoma of the lung in women. J Natl Cancer Inst 1994;86:869–70.
11. Liu Y, Inoue M, Sobue T, Tsugane S; for the JPHC Study Group. 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 2005;117:662–6.
12. Kreuzer M, Gerken M, Heinrich J, Kreienbrock L, Wichmann H-E. Hormonal factors and risk of lung cancer among women? Int J Epidemiol 2003;32:263–71.
13. Schabath MB, Wu X, Vassilopoulou-Sellin R, Vaporciyan AA, Spitz MR. Hormone replacement therapy and lung cancer risk: a case-control analysis. Clin Cancer Res 2004;10:113–23.
14. Ettinger B, Friedman GD, Bush T, Quesenberry CP. Reduced mortality associated with long-term postmenopausal estrogen therapy. Obstet Gynecol 1996;87:6–12.
15. Olsson H, Bladstrom A, Ingvar C. Are smoking-associated cancers prevented or postponed in women using hormone replacement therapy? Obstet Gynecol 2003;102:565–70.
16. Adami H-O, Persson I, Hoover R, Schairer C, Bergkvist L. Risk of cancer in women receiving hormone replacement therapy. Int J Cancer 1989;44:833–9.
17. Blackman JA, Coogan PF, Rosenberg L, et al. Estrogen replacement therapy and risk of lung cancer. Pharmacoepidemiol Drug Safety 2002;11:561–7.
18. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–33.
19. Wu AH, Yu MC, Thomas CC, Pike MC, Henderson BE. Personal and family history of lung disease as risk factors for adenocarcinoma of the lung. Cancer Res 1998;48:7279–84.
20. Elliot AM, Hannaford PC. Use of exogenous hormones by women and lung cancer: evidence from the Royal College of General Practitioners' Oral Contraception Study. Contraception 2006;73: 331–5.
21. Writting Group for the Women's Health Initiative Investigators. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. The Women's Health Initiative randomized controlled trial. JAMA 2004;291:1701–12.
22. Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy. Annual trends and response to recent evidence. JAMA 2004;291:47–53.
23. Drug Topics. Drugs by units in the United States in specific years. Available from: http://www.drugtopics.com/drugtopics/. Accessed 2007 Mar 29.
24. Calle EE. The American Cancer Society Nutrition Survey—rationale, study design, and baseline characteristics. Cancer 2002;94:500–11.
25. Garfinkel L. Selection, follow-up, and analysis in the American Cancer Society prospective studies. Monogr Natl Cancer Inst 1985;67: 49–52.
26. Calle EE, Terrell DD. Utility of the National Death Index for ascertainment of mortality among Cancer Prevention Study II participants. Am J Epidemiol 1993;137:235–41.
27. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet 1997;350: 1047–3.
28. Henderson BE, Ross RK, Pike MC, Casagrande JT. Endogenous hormones as a major factor in human cancer. Cancer Res 1982;42: 3232–9.
29. Cagle PT, Mody DR, Schwartz MR. Estrogen and progesterone receptors in bronchogenic carcinoma. Cancer Res 1990;20:6632–5.
30. Marquez-Garban DC, Chen HW, Fishbein MC, Goodglick L, Pietras RJ. Estrogen receptor signaling pathways in human non-small cell lung cancer. Steroids 2007;72:135–43.