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Reproductive factors, hormone use and risk of lung cancer in postmenopausal women, the Nurses' Health Study

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Abstract

Background—There is increasing evidence suggesting that female hormones may play a significant role in lung cancer (LC) development. We evaluated the associations between reproductive factors, exogeneous hormone use, and LC incidence in the Nurses' Health Study (NHS).

Methods—We assessed age at menopause, age at menarche, type of menopause, parity, age at first birth, postmenopausal hormone (PMH) use and past oral contraceptive use in 107,171 postmenopausal women. Cox models were used to estimate the hazard ratios (HR) for each exposure, adjusted for smoking and other covariates.

Results—We identified 1,729 LC cases during follow up from 1984 to 2006. Menopause onset before 44 years of age (HR=1.39, 95%CI 1.14-1.70) and past oral contraceptive use for greater than 5 years (HR=1.22, 95%CI 1.05-1.42) were associated with increased LC risk. These associations were strongest in current smokers and small cell histology. In never smokers, increased parity was associated with decreased risk among parous women (*p*-trend=0.03), whereas in current smokers, older age at first birth was associated with increased risk (*p*-trend=0.02). PMH use was not associated with overall LC incidence. However, nonsignificant results of increased risk in adenocarcinoma were seen with current PMH use.

Conclusions—Our findings suggest female hormones may influence lung carcinogenesis though the effect is likely modest, varied by histologic subtype and altered by smoking.

Impact—Further investigation of the pathophysiology of female hormones in LC subtypes and their interaction with smoking will lead to better understanding of lung carcinogenesis.

Keywords

lung cancer; reproductive factors; hormone replacement therapy; epidemiology

Background

Lung cancer is the leading cause of cancer mortality in US women. The American Cancer Society estimates that 70,490 women will die of lung cancer in 2009, which exceeds combined

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breast and colorectal cancer mortality in women [1]. There is increasing evidence that lung cancers in women are biologically distinct from those of men with the observation that they exhibit different distribution of histologic subtypes and molecular characteristics. Women are more likely to develop adenocarcinoma compared to men, especially among never smokers [2,3]. In comparison to men, women with lung cancer are also more likely to be lifelong nonsmokers [4]. Moreover, adenocarcinoma in women are more likely to harbor epidermal growth factor receptor (EGFR) mutations [5,6] and thus more likely to respond to EGFR tyrosine kinase inhibitors [7-9].

These gender differences raise the question of whether female hormones could play a role in lung carcinogenesis. In fact, estrogen-β and progesterone receptors have been found on lung cancer cells [10,11], and in a preclinical study by Stabile *et al*, a significant increase in cellular proliferation was seen in lung cancer-derived cell lines when they were incubated with β-estradiol and this was inhibited by anti-estrogens [10,12]. Similar results have been seen in lung adenocarcinoma mouse models in which ovariectomized mice treated with estradiol developed higher tumor counts and volume compared to untreated mice [13].

These findings suggest that a woman's reproductive history and exogenous hormone use could affect her risk of developing lung cancer. Several epidemiologic studies have investigated the association between postmenopausal hormone use and lung cancer incidence. However, results have been conflicting. While several studies reported decreased risk with hormone replacement therapy [14-18], others reported no effect [19-22] and a few others reported a trend towards increased risk [23-25]. Many have also investigated the effect of reproductive factors but these results have been inconsistent [16,19,20,22-29]. Most of these studies were retrospective in design and varying adjustment for covariates may have contributed to the inconsistent results. Thus our aim was to conduct a prospective and comprehensive analysis of reproductive factors and exogeneous hormone use in relation to lung cancer incidence in the Nurses' Health Study (NHS). We further evaluated these associations separately by smoking status and histologic subtypes.

Methods

Study Population

The Nurses' Health Study was established in 1976 with 121,700 female US nurses of ages between 30 and 55 years who responded to the initial mailed questionnaire. The women were asked questions regarding their medical history and lifestyle which included detailed reproductive and hormone use information as well as smoking history. Follow up questionnaires have been sent every two years to update information regarding exposure status and to identify newly diagnosed medical conditions, and the response rate has been at least 90% for each cycle.

We have previously shown that fruit and vegetable consumption was associated with lower risk of lung cancer among women [30], thus we used 1984 as the baseline year since this was the first cycle in which diet assessment with extensive questions on fruits and vegetables was available. At baseline, we included women who were postmenopausal and had not reported a diagnosis of cancer (except non-melanoma skin cancers) and women entered analysis during follow-up when they reached menopause. Women were classified as postmenopausal at the age when natural menopause or bilateral oophorectomy occurred. For women whose periods stopped after a hysterectomy or unilateral oophorectomy, we classified them as postmenopausal at age 54 if a current smoker or 56 if a nonsmoker which were the ages by which 90% of NHS participants with a natural menopause had become postmenopausal.

The NHS is approved by the Brigham and Women's Hospital Institutional Review Board in Boston, Massachusetts. This investigation was also approved by Tufts University Institutional Review Board in Boston, Massachusetts.

Case ascertainment

Lung cancers were reported by the participants or identified on their death certificates and they were subsequently confirmed by hospital records and pathology reports. The cases were classified as confirmed only if a pathology report indicated that the lesion was a primary lung tumor. The confirmed lung cancer cases were then classified by predominant histologic subtype. Of the self-reported cases, 88% were confirmed with medical records and an additional 6% were confirmed by death certificates. All self-reported lung cancers were included in the primary analyses since results were very similar when limited to cases confirmed by medical records. Analyses by histologic subtype included only those confirmed by medical record review.

During the 22-year follow up, 1,729 incident lung cancer cases were identified. Of the 1,505 cases for which histology information was available, 47% were adenocarcinoma, 18% small cell carcinoma, 17% squamous cell carcinoma, 5% large cell, 10% unspecified non-small cell lung cancer and 3% other histologies including carcinoid and sarcoma. The histology distribution is comparable to SEER data reported for female lung cancer [31].

There were 8% never smokers, 45% former smokers and 47% current smokers among the cases as determined by their smoking status on the biennial questionnaire prior to lung cancer diagnosis. Of the 138 cases among never smokers, adenocarcinoma was the predominant histologic subtype in 81 cases (62%), and there were no cases with small cell histology.

Reproductive and hormonal exposures

The exposure variables assessed in this analysis were: age at menarche, age at menopause, type of menopause, parity, age at first birth, oral contraceptive (OCP) use and postmenopausal hormone (PMH) use.

Age at menarche was reported on the initial 1976 questionnaire and number of pregnancies lasting more than 6 months were assessed from 1976 through the 1984 questionnaire and reconfirmed in 1996. In each biennial questionnaire, women were asked whether their menstrual periods had stopped, age at which they stopped and whether the reason was natural or surgical. PMH and OCP use were first assessed on the initial 1976 questionnaire and were updated in each biennial questionnaire which asked details regarding current or past use, duration of use and type of hormones used. At each 2-year follow up cycle, we calculated total duration of use and time since last use. We stopped collecting additional OCP information in 1984 when less than 1% of the premenopausal women were currently using the medication. Missing information regarding exposure variables was included as a separate category.

Smoking exposure and other covariates

Participants were asked on the initial questionnaire whether they were current or former smokers and if so, their age at initiation. Former smokers were asked the age at which they discontinued smoking, and current smokers were asked to report their average number of cigarettes smoked per day. Participants with missing smoking status were excluded at baseline. Smoking status and quantity of cigarettes have been updated every two years. In 1982, participants were asked for information regarding environmental tobacco exposure, including whether one or both parents smoked, number of years living with someone who smoked, and whether exposed to smoke at work and/or at home. Other covariates included body mass index, calculated each questionnaire cycle from current weight and from height reported at baseline,

and dietary intake assessed in alternate cycles with a food frequency questionnaire that included 15 fruits and 30 vegetables. The validity of the FFQ has been assessed and published previously [32,33].

Statistical Analysis

We accumulated person-years beginning at the return of the 1984 questionnaire or the first questionnaire on which a participant was classified as postmenopausal. Follow up ended with a report of lung or any other cancer other than non-melanoma skin cancers, death, or end of follow up on June 1, 2006. Person-years contributed to exposure categories in each biennial follow-up cycle based upon the most recent questionnaire information. Women did not contribute person-years in cycles when their smoking status was unknown.

Cox proportional hazards models were used to estimate hazard ratios (HR) of lung cancer in each exposure category compared to a reference category. For continuous variables, *p*-values for linear trend were calculated. The multivariate models included all assessed risk factors and covariates. Risk estimates were obtained separately from analyses stratified by smoking status (never, former, current) and histology subtypes (adenocarcinoma, squamous cell carcinoma and small cell carcinoma).

Results

The characteristics of participants over follow-up are shown in Table 1 by PMH and OCP use. We analyzed 107,171 postmenopausal women from 1984-2006, during which a total of 1,590,432 person-years were accumulated and in which 14% were current smokers, 41% former smokers and 45% never smokers. The participants were primarily Caucasian and their mean age over follow-up was 63 (range 38-87). After adjusting for age, current PMH users were more likely to have used OCP, more likely to have had surgical menopause, less likely to be current smokers, and had a lower mean BMI. Women who used OCP for more than 5 years were less likely to be nulliparous, although the mean number of children among parous women was similar across the OCP use duration categories. Current smokers were younger at menopause compared to never smokers, but parity, age at first birth and age at menarche did not differ by smoking status (data not shown). The age-adjusted crude incidence of lung cancer in this cohort was 109 per 100,000 person-years.

Among all women in our analysis, onset of menopause before 44 years of age when compared with onset at 48-49 (HR=1.39, 95% CI 1.14-1.70) and oral contraceptive use for more than 5 years when compared to never OCP users (HR=1.22, 95% CI 1.05-1.42) were associated with increased risk of lung cancer incidence after adjusting for smoking, fruit/vegetable intake, body mass index, environmental smoking exposure and other exposure variables (Table 2). The increased risk with younger age at menopause was also seen when restricted to natural menopause (data not shown). When assessed separately by smoking status, these associations were primarily evident in current smokers. In regards to parity, greater number of children was associated with decreased risk among parous women (*p*-trend=0.03) in never smokers whereas older age at first birth was associated with increased risk (*p*-trend=0.02) in current smokers. Risk of lung cancer was not associated with PMH use, age at menarche, or type of menopause in the overall study population or within categories of smoking status.

When assessed by histologic subtypes, risk of small cell carcinomas was increased with younger age at menopause (*p*-trend=0.008) and more than 5 years of OCP use (HR=1.71, 95% CI 1.20-2.44) and decreased with greater number of children among parous women (p trend=0.01). A decreased risk (HR=0.56, 95% CI 0.28-1.10) was also observed for nulliparous versus parous women, though the small number of nulliparous women in this subgroup make this result unstable (Table 3). Though no significant associations were seen for squamous cell

or adenocarcinoma, an increased risk with older age at first birth appeared limited to adenocarcinoma.

We examined PMH use in more detail in relation to risk of specific lung cancer histologic subtypes (Table 4). No statistically significant results were observed, though patterns were observed. For adenocarcinoma, risk was increased among current PMH users and among those with five or more years of use for both estrogen only and estrogen plus progestin formulations. For squamous carcinoma, a trend of increased risk was seen with five or more years of estrogen plus progestin use.

Discussion

In this analysis of reproductive factors and lung cancer incidence, younger age at menopause and longer duration of oral contraceptive use were associated with increased risk. These associations were strongest among current smokers and small cell histology, which likely reflects the high proportion of current smokers within this histologic subtype. Increased risk was also seen with fewer children among never smokers and older age at first birth among current smokers.

The literature on hormonal factors and lung cancer has expanded in the past several years, reflecting the increased interest in this field. However, the methods of study design are heterogeneous across studies, which may explain the inconsistent reports in the literature. Despite the inconsistencies, several studies have reported an inverse association between age at menopause and lung cancer incidence. In a prospective analysis of the Shanghai Women's Health Study with approximately 75,000 participating Chinese women who were lifetime non-smokers, the authors reported higher lung cancer risk with younger age at menopause [26]. Other population based studies have also reported similar trends albeit not statistically significant [24,27-29]. However, there also are reports of null association [16,22,23] and one report of decreased risk with younger age at menopause [25].

Regarding parity, two prospective cohort studies of never smokers have reported an inverse association in which decreased risk was seen with increasing parity [23,26]. This is consistent with our results in which the inverse relationship was seen primarily in never smokers. The role of parity in other studies which include smokers is less clear. In regards to the age at first birth, literature is inconsistent with reports of decreased [19,22] and increased [23] risk with increasing age at first birth as well as reports of no significant association [16,26,28,29]. The association with the use of oral contraceptives is inconsistent as well with a few reports of decreased risk [22,24]. However, most studies report a null association [16,19,20,25,26].

Our findings suggest that endogenous hormones during premenopausal years may have a protective role in lung cancer development. This is evident by the increased lung cancer risk with younger age at menopause and longer use of oral contraceptives in which the contraceptive mechanism is by suppressing ovulation and the release of endogenous hormones [34]. The protective role appears to be greater among smokers and a possible mechanism may be the interaction between estrogen and cigarette smoke metabolism. *CYP1A1 and CYP1B1*, members of the cytochrome P450 family of enzymes involved in phase I drug metabolism, are induced by cigarette smoking and they activate cigarette smoke carcinogens such as polycyclic aromatic hydrocarbons and also participate in estradiol metabolism [35]. Several investigators have hypothesized that this interaction may be the mechanism by which smokers are found to have lower estrogen levels compared to nonsmokers [36-38]. Conversely, there are reports of *CYP1A1* and *CYP1B1* upregulation by estrogen-α and estrogen-β receptors [35,39,40]. The effect of estrogen on phase II metabolism enzymes is not clear although increased glutathione S-transferase (*GSTT1*) mRNA expression has been associated with higher estradiol levels

[35]. This suggests that estrogen may influence the metabolism of smoking constituents and lead to differential lung cancer outcomes among smokers.

Another possible mechanism for the protective effect of premenopausal endogenous hormones may be the role of progesterone in lung cancer development. In a preclinical study by Ishibashi *et al*, cellular proliferation was inhibited when lung cancer cell lines with progesterone receptors were incubated with progesterone [11]. However, the literature on progesterone in lung cancer is limited and the role of progesterone and its interaction with estrogen in lung cancer remains unclear.

In regards to PMH use, we did not detect a significant association between PMH use and overall lung cancer incidence, although differential trends were seen in the various histologic subtypes. While reproductive factors reflect the effect of hormonal exposure during premenopausal years, the use of hormone replacement therapy exerts its effect during postmenopausal years. As described earlier, the literature on PMH use and lung cancer is conflicting with reports of protective, null and harmful associations [14-25]. More recently, the Women's Health Initiative investigators reported an increase in mortality and a nonsignificant increase in incidence of non-small cell lung cancer in the women who were randomized to the estrogen and progestin combination arm [41]. A similar trend has been reported in a prospective cohort study of never smokers in which the majority of cases were adenocarcinoma [23] and in two other case-control studies in which the primary outcome was adenocarcinoma [24,25]. Also, the VITAL (Vitamins and Lifestyle) study recently reported an increased risk of lung cancer incidence with estrogen and progestin use [42]. We did not detect a significant increased risk with estrogen and progestin use although a nonstatistically significant trend of increased risk was detected for squamous and adenocarcinoma. These findings in addition to the results of our analysis suggest that the role of postmenopausal hormones likely differ from that of premenopausal reproductive hormones and that the effect may vary in the different histologic subtypes.

There are many challenges in elucidating the role of hormones in lung carcinogenesis. One of the challenges is the fact that there are many situations in which a hormonal function could be altered. For instance, the action of the same hormone may vary in pre- versus postmenopausal women, smokers versus never smokers, and in the pathogenesis of tumors of various histologic subtypes. Furthermore, the effect of hormones may also depend on the receptor status of lung cancer cells. In a study by Schwartz *et al*, the investigators found a protective association between PMH use and lung cancer but the association was seen primarily in lung cancers that harbored estrogen receptors [16]. This suggests that the role of reproductive hormones as well as exogenous hormones may be restricted to those cancers that possess the receptors.

There are several strengths in this study. First, this study is prospective in design, which avoids the biases associated with retrospective studies, and the large number of cases and participants with long duration of follow up have allowed us to perform various subgroup analyses. Although the number of exposure variables and subgroups in this study increases the likelihood of chance findings, all analyses were hypothesis-driven and exposure variables were chosen *a priori*, thus no adjustment was made for multiple comparisons. Another strength of this study is that information on exposures and smoking variables was updated every two years, which reduces misclassification bias. A limitation is the small number of cases among never smokers. Accordingly, the lack of significant findings in never smokers may be due to the small number of cases.

In conclusion, the results of our study add to the increasing body of literature which indicates that female hormones may influence lung carcinogenesis. Their role is likely modest, especially in the presence of powerful risk factors such as smoking. However, additional research of this

topic is warranted as it may lead to better understanding of lung cancer biology and possibly to development of novel therapeutic strategies. In order to achieve this goal, an integrative approach will be necessary spanning from molecular and clinical epidemiology research, to clinical prevention and therapeutic trials.

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Table 1

Age-adjusted characteristics by postmenopausal hormone and past oral contraceptive use among postmenopausal women in the Nurses' Health Study, 1984-2006 [a]

			PMH use			OCP duration
	never	past	current	never	<5 yrs	>5 yrs
Age (y)	62.2(7.0)	65.8(7.2)	61.7(7.3)	65.5(6.8)	60.9(7.4)	61.5(7.0)
PMH						
Never (%)				33	22	23
Past (%)				23	28	26
Current (%)				27	40	42
PMH duration (y)		4.8(5.4)	10.3(7.5)			
Past OCP use (%)	33	45	48			
Nulliparous (%)	5	6	6	7	4	3
Parity [b]	3.3(1.5)	3.1(1.4)	3.1(1.3)	3.2(1.5)	3.2(1.4)	3.2(1.4)
Age at first birth (y)	25.5(3.5)	25.1(3.4)	25.0(3.2)	25.5(3.5)	25.2(3.4)	24.7(3.1)
Age at menarche (y)	12.6(1.4)	12.5(1.4)	12.6(1.4)	12.6(1.4)	12.5(1.4)	12.6(1.4)
Age at menopause (y)	50.3(3.8)	48.3(5.2)	48.8(5.0)	49.0(4.9)	49.1(4.6)	49.7(4.0)
Natural menopause (%)	79	56	46	59	56	64
Surgical menopause (%)	12	35	44	28	33	26
Smoking						
Never (%)	44	41	45	46	42	42
Past (%)	39	43	44	39	45	44
Current (%)	17	16	11	15	13	15
BMI (kg/m^2)	26.5(5.1)	26.1(4.9)	25.2(4.3)	26.1(4.8)	25.9(4.8)	25.6(4.7)
Fruit intake (servings/day)	1.9(0.7)	1.9(0.7)	1.9(0.7)	1.9(0.7)	1.9(0.7)	1.9(0.7)
Vegetable intake (servings/day)	2.2(0.6)	2.2(0.6)	2.3(0.6)	2.2(0.6)	2.3(0.6)	2.2(0.6)
Regular smoking exposure at work (%) [c]	25	25	24	22	26	29
Regular smoking exposure at home (%) [c]	21	20	17	18	26	22
Both parents smoked (%) [c]	13	15	15	12	17	17
Living >20yrs with someone	36	32	28	32	29	32

		PMH use			OCP duration	
	never	past	current	never	<5 yrs	>5 yrs
who smoked (%) [c]						

Abbreviations: PMH, postmenopausal hormone; OCP, oral contraceptive; Y, years; BMI, body mass index

[a] Values are presented as means or percentages; standard deviations are presented in parentheses when indicated

[b] Among parous women only

[c] Smoking exposure at home and work assessed at baseline only

Table 2

Hazard ratios of lung cancer by reproductive factors and postmenopausal hormone use in postmenopausal women, 1984-2006. Stratified analysis by smoking status

	All women (cases=1729)		Never smokers (cases=138)		Former smoker (cases=782)		Current smokers (cases=809)	
	cases	HR(95% CI)	cases	HR(95% CI)	cases	HR(95% CI)	cases	HR(95% CI)
Age at menopause								
< 44	229	1.39 (1.14-1.70)	18	1.42(0.69-2.95)	78	1.08 (0.79-1.48)	133	1.76 (1.32-2.34)
44-47	258	1.06 (0.89-1.26)	15	0.88(0.43-1.80)	111	1.03 (0.79-1.34)	132	1.16 (0.89-1.50)
48-49	244	1.0	16	1.0	115	1.0	113	1.0
50-51	587	1.04 (0.88-1.22)	52	1.17(0.64-2.15)	261	0.97 (0.76-1.23)	274	1.16 (0.91-1.48)
52+	386	0.94 (0.79-1.10)	37	0.78(0.43-1.44)	204	0.96 (0.76-1.22)	145	0.99 (0.77-1.28)
p-trend		0.0004		0.22		0.33		0.001
Age at menarche								
≤11	377	1.04 (0.91-1.19)	29	0.85(0.53-1.36)	181	1.17 (0.96-1.43)	167	0.97 (0.79-1.19)
12	421	0.97 (0.85-1.10)	32	0.79(0.50-1.24)	190	1.02 (0.84-1.24)	199	0.98 (0.81-1.19)
13	523	1.0	48	1.0	227	1.0	248	1.0
14	217	0.99 (0.84-1.16)	20	1.00(0.59-1.69)	94	0.95 (0.74-1.21)	103	1.08 (0.85-1.37)
15+	174	1.05 (0.88-1.25)	9	0.67(0.32-1.36)	81	1.08 (0.83-1.39)	84	1.14 (0.88-1.47)
p-trend		0.84		0.88		0.43		0.29
Type of menopause								
natural	982	1.0	70	1.0	458	1.0	454	1.0
0 ovaries removed[b]	184	1.19 (0.99-1.42)	16	1.08(0.59-1.95)	81	1.12 (0.86-1.45)	87	1.30 (0.99-1.70)
1	68	1.29 (0.99-1.67)	8	1.67(0.77-3.62)	33	1.30 (0.89-1.88)	27	1.17 (0.77-1.76)
2	265	1.06 (0.90-1.25)	29	1.33(0.78-2.26)	109	1.02 (0.80-1.30)	127	1.03 (0.80-1.32)
Parity								
nulliparous	104	0.97(0.79-1.18)	14	1.66(0.94-2.93)	47	1.08(0.80-1.46)	43	0.75(0.54-1.03)
parous	1567	1.0	124	1.0	706	1.0	737	1.0
1-2 children	510	1.0	54	1.0	209	1.0	247	1.0
3-4	771	1.09(0.97-1.22)	54	0.70(0.48-1.03)	367	1.29(1.08-1.53)	358	1.00(0.84-1.18)
5+	278	1.00(0.86-1.17)	16	0.50(0.28-0.88)	130	1.18(0.94-1.48)	132	0.93(0.75-1.16)
p-trend [c]		0.87		0.03		0.16		0.30

	All women (cases=1729)		Never smokers (cases=138)		Former smoker (cases=782)		Current smokers (cases=809)	
	cases	**HR(95% CI)**	**cases**	**HR(95% CI)**	**cases**	**HR(95% CI)**	**cases**	**HR(95% CI)**
Age at first birth								
< 26 yrs	951	1.0	73	1.0	436	1.0	442	1.0
26-30	461	1.03(0.91-1.15)	36	0.91(0.60-1.38)	205	0.95(0.80-1.13)	222	1.12(0.95-1.33)
> 30	154	1.20(1.01-1.43)	15	1.30(0.73-2.31)	65	1.10(0.84-1.44)	74	1.38(1.06-1.78)
p-trend [c]		0.06		0.66		0.60		0.02
PMH use								
never	436	1.0	34	1.0	184	1.0	218	1.0
past	440	0.91 (0.79-1.04)	32	0.90(0.54-1.50)	201	0.83 (0.67-1.02)	207	0.96 (0.78-1.18)
Current	455	0.99 (0.86-1.14)	46	1.00(0.61-1.63)	228	0.96 (0.77-1.18)	181	1.02 (0.82-1.27)
OCP use								
never	1059	1.0	96	1.0	471	1.0	492	1.0
past	626	1.10(0.99-1.22)	39	0.88(0.58-1.33)	290	1.15 (0.98-1.35)	297	1.06 (0.90-1.25)
<5 yrs	358	1.06 (0.93-1.21)	26	0.96(0.59-1.54)	166	1.13 (0.93-1.37)	166	1.00 (0.82-1.21)
>5 yrs	232	1.22 (1.05-1.42)	10	0.72(0.36-1.41)	106	1.25 (1.00-1.56)	116	1.28 (1.03-1.60)
p-trend		0.07		0.33		0.07		0.17

Abbreviations: HR, hazard ratio; CI, confidence interval; PMH, postmenopausal hormone; OCP, oral contraceptive

[a] Adjusted by: age at menopause, age at menarche, parity, type of menopause, PMH use, OCP use, smoking status, age at start smoking, cigarettes per day, time since quitting, fruit/vegetable intake, body mass index, environmental smoking exposure (parents smoking, years living with someone who smokes, exposure to smoking at work, exposure to smoking at home)

[b] Hysterectomy only

[c] Among parous women only

Table 3

Hazard ratios of lung cancer histology subtypes by reproductive factors in postmenopausal women, 1984-2006 [a]

		Adeno carcinoma (n=706)		Squamous carcinoma (n=253)		Small cell carcinoma (n=264)
	cases	HR(95% CI)	cases	HR (95% CI)	cases	HR (95% CI)
Age at menopause						
< 44	80	1.16 (0.84-1.62)	31	1.12 (0.68-1.84)	33	1.63 (0.98-2.70)
44-47	117	1.26 (0.95-1.66)	36	0.79 (0.51-1.23)	39	1.04 (0.66-1.63)
48-49	89	1.0	48	1.0	40	1.0
50-51	260	1.29 (0.99-1.70)	71	0.69 (0.46-1.02)	96	1.07 (0.71-1.61)
52+	152	1.00 (0.78-1.31)	67	0.89 (0.60-1.31)	56	0.88 (0.57-1.33)
p-trend		0.21		0.49		0.008
Age at menarche						
≤11	165	1.18 (0.96-1.45)	55	0.94 (0.67-1.32)	56	1.10 (0.77-1.58)
12	170	0.98 (0.80-1.20)	57	0.78 (0.56-1.10)	79	1.29 (0.93-1.80)
13	208	1.0	89	1.0	71	1.0
14	91	1.05 (0.82-1.34)	24	0.62 (0.39-0.98)	35	1.21 (0.80-1.82)
15+	72	1.09 (0.83-1.43)	26	0.92 (0.59-1.44)	20	0.93 (0.56-1.54)
p-trend		0.56		0.54		0.64
Type of menopause						
natural	393	1.0	160	1.0	164	1.0
0 ovaries removed [b]	76	1.04 (0.80-1.37)	32	0.75(0.43-1.31)	34	1.48(0.96-2.26)
1	33	1.36 (0.94-1.98)	9	1.22(0.60-2.50)	7	0.83(0.38-1.83)
2	120	1.24 (0.97-1.59)	16	0.87(0.55-1.37)	26	0.66(0.41-1.07)
Parity						
nulliparous	44	1.05(0.77-1.43)	10	0.60(0.31-1.14)	9	0.56(0.28-1.10)
parous	637	1.0	238	1.0	245	1.0
1-2 children	51	1.0	14	1.0	91	1.0
3-4	197	1.10(0.92-1.31)	66	1.18(0.88-1.60)	114	0.84(0.64-1.12)

		Adeno carcinoma (n=706)		Squamous carcinoma (n=253)		Small cell carcinoma (n=264)
	cases	HR(95% CI)	cases	HR (95% CI)	cases	HR (95% CI)
5+	98	0.86(0.67-1.10)	46	1.12(0.77-1.65)	40	0.78(0.53-1.14)
p-trend [c]		0.22		0.19		0.01
Age at first birth						
< 26 yrs	391	1.0	139	1.0	151	1.0
26-30	181	0.99(0.83-1.19)	76	1.15(0.86-1.53)	78	1.08(0.81-1.43)
> 30	68	1.31(1.00-1.72)	22	1.08(0.68-1.72)	16	0.75(0.44-1.29)
p-trend [c]		0.12		0.43		0.91
OCP duration						
Never	430	1.0	154	1.0	157	1.0
past	258	1.05(0.88-1.24)	93	1.16(0.87-1.53)	101	1.21(0.92-1.59)
<5 yrs	160	1.09 (0.90-1.33)	51	1.09 (0.78-1.53)	50	0.99(0.70-1.39)
>5 yrs	81	0.99 (0.77-1.27)	37	1.37 (0.93-2.00)	46	1.71 (1.20-2.44)
p-trend		0.82		0.25		0.08

Abbreviations: HR, hazard ratio; CI, confidence interval; PMH, postmenopausal hormone; OCP, oral contraceptive

[a]Adjusted by: age at menopause, age at menarche, parity, type of menopause, PMH use, OCP use, smoking status, age at start smoking, cigarettes per day, time since quitting, fruit/vegetable intake, body mass index, environmental smoking exposure (parents smoking, years living with someone who smokes, exposure to smoking at work, exposure to smoking at home)

[b]Hysterectomy only

[c]Among parous women only

Table 4

Hazard ratios of lung cancer histology subtypes by postmenopausal hormone use in postmenopausal women, 1984-2006 [a]

		All lung cancer (n=1729)		Adeno carcinoma (n=706)		Squamous carcinoma (n=253)		Small cell carcinoma (n=264)
	cases	HR (95% CI)	cases	HR (95% CI)	cases	HR (95% CI)	cases	HR (95% CI)
PMH use								
never	436	1.0	171	1.0	76	1.0	78	1.0
past	440	0.91(0.79-1.04)	178	0.93(0.74-1.16)	68	0.87 (0.61-1.24)	71	0.89 (0.63-1.26)
current	455	0.99(0.86-1.14)	224	1.18(0.95-1.47)	52	0.76 (0.52-1.12)	57	0.86 (0.60-1.25)
PMH type								
never	436	1.0	171	1.0	76	1.0	78	1.0
E	486	0.99(0.85-1.14)	223	1.09(0.87-1.37)	54	0.73(0.49-1.09)	65	0.91(0.63-1.33)
E+P	249	1.00(0.85-1.18)	106	1.07(0.83-1.38)	44	1.06(0.71-1.57)	33	0.88(0.57-1.36)
PMH duration								
never	436	1.0	171	1.0	76	1.0	78	1.0
E <5yrs	139	0.97(0.80-1.19)	51	0.91(0.66-1.25)	20	0.82(0.49-1.36)	26	1.11(0.70-1.77)
≥5yrs	347	0.99(0.84-1.17)	172	1.21(0.94-1.56)	34	0.66(0.41-1.05)	39	0.78(0.50-1.22)
E+P <5yrs	85	0.88(0.70-1.12)	35	0.91(0.62-1.32)	14	0.85(0.47-1.53)	14	0.94(0.52-1.69)
>5yrs	164	1.08(0.89-1.30)	71	1.17(0.88-1.57)	30	1.22(0.78-1.91)	19	0.85(0.50-1.44)

Abbreviations: HR, hazard ratio; CI, confidence interval; PMH, postmenopausal hormone; E+P, estrogen + progestin combination; E, unopposed estrogen; OCP, oral contraceptive

[a] Adjusted by: age at menopause, age at menarche, parity, type of menopause, PMH use, OCP use, smoking status, age at start smoking, cigarettes per day, time since quitting, fruit/vegetable intake, body mass index, environmental smoking exposure (parents smoking, years living with someone who smokes, exposure to smoking at work, exposure to smoking at home)