Research Article

Cancer Epidemiology, Biomarkers & Prevention

Reproductive and Hormonal Factors and Lung Cancer Risk in the NIH-AARP Diet and Health Study Cohort

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Abstract

Background: Lung cancer exhibits unique patterns among women including high adenocarcinoma rates among nonsmokers. Inconsistent findings about hormonal factors on risk may reflect incomplete control for confounding, misclassification of exposures, or insufficient attention to variation by histology.

Methods: Among 185,017 women, ages 50 to 71 years, recruited during 1995 and 1996 for the NIH-AARP (American Association of Retired Persons) Diet and Health Study, we identified 3,512 incident lung cancers (including 276 in never smokers) in follow-up through December 2006. Multivariable Cox proportional hazards models estimated relative risks (RR) and 95% CIs for self-reported hormonally related risk factors.

Results: After adjustment for smoking and other confounders, subjects with late menarche were at reduced risk, with the association specific for adenocarcinomas (RR = 0.72 for menarche 15+ vs. <11, $P_{trend} < 0.01$). Subjects with early ages at ovarian cessation (either from natural menopause or bilateral oophorectomy) were at an increased risk for adenocarcinomas and squamous cell tumors, but the associations were strongest for smokers, suggesting either residual confounding or an enhanced effect of menopausally related factors among subjects with decreased endogenous estrogens. In contrast, we saw no relationships of risk with either parity, age at first birth, or exogenous hormone use.

Conclusions: Elevated levels of hormones may adversely affect lung function early in life while assisting with cellular and immunologic responses later in life. Additional attention toward the role of hormonal factors may further our understanding of lung carcinogenesis.

Impact: Our findings provide some support for a role of hormonal factors in the etiology of lung cancer, although the mechanisms appear complicated. *Cancer Epidemiol Biomarkers Prev; 20(5); 900–11. ©2011 AACR.*

Introduction

Although cigarette smoking is the major cause of lung cancer in women, approximately 10% to 15% of these cancers occur among nonsmokers, suggesting the role of other factors (1). Recent attention has focused on various hormonal factors, prompted by consistently observed sex differences by histology including especially high rates of adenocarcinomas among nonsmoking women (2).

There is in fact a fair amount of laboratory evidence supporting a potential role of hormones in the etiology of lung cancer, including abundant expression of estrogen and progesterone receptors in normal lung tissue and lung tumor cell lines (3). However, only a relatively limited number of epidemiologic studies have focused on effects of hormonal risk factors for lung cancers in women. Several recent studies have reported reduced risks related to multiparity (4–7) and late ages at first birth (8, 9), menarche (10, 11) and menopause (7, 10–13), and increased risks among women experiencing bilateral oophorectomies (11, 14). However, the findings have been far from consistent across studies.

Difficulties in interpreting these relationships may partially reflect that women who experience early menstrual cessation have frequently been prescribed, oftentimes for extended periods of time, exogenous hormones, an exposure that has also been found in some studies to be inversely associated with lung cancer risk (9, 15–20). However, not all studies have confirmed this relationship, including the large Women's Health Initiative clinical trial (21, 22).

Some of the observed inconsistencies about the role of hormonal factors in lung cancer etiology may also reflect incomplete control for confounding (including by smoking), misclassification of exposures, or failure to assess variation in effects by histologic subtypes. To address these complexities in detail, we took advantage of

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doi: 10.1158/1055-9965.EPI-10-1325

comprehensive data and follow-up from the large NIH-AARP (American Association for Retired Persons) Diet and Health Study, an investigation that included prospective data on over 3,500 incident cases of lung cancer.

Methods

Study population

The NIH-AARP Diet and Health Study Cohort was established in 1995 and 1996 when a questionnaire requesting information on demographic characteristics, dietary intake, and health-related behaviors was sent to 3.5 million AARP members (23). Recipients of the questionnaire included members aged 50 to 71 years who resided in 1 of 6 U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) or 2 metropolitan areas (Atlanta, GA; Detroit, MI). A total of 617,119 persons (17.6%) returned the questionnaire, with 566,402 (16.2%) satisfactorily completing it. After excluding participants who had proxies complete their baseline questionnaires ($n = 15{,}760$) and subjects who were male ($n = 325{,}174$), 225,468 potentially eligible women remained. The Special Studies Institutional Review Board of the National Cancer Institute approved this study.

Exposure ascertainment

Female study subjects were asked to provide information on a variety of reproductive and hormonal factors, according to defined response categories. To determine whether subjects were menopausal, they were asked at what age they had their last menstrual period, and, if periods had stopped, whether menopause was natural or due to surgery or radiation/chemotherapy. Subjects were also asked whether they had a hysterectomy or surgery that involved removal of 1 or both ovaries. For cigarette smoking, subjects were asked whether they had ever smoked 100 or more cigarettes during their entire lifetime. Ever smokers were then asked if they currently smoked, and, if not, when they stopped (within last year or 1–4, 5–9, 10+ years ago) and how many cigarettes per day they usually smoked.

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

On the basis of 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 8 areas from which study subjects were derived. 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 (24). The cancer registry ascertainment area was recently expanded to include 2 additional states (Texas and Arizona) to capture cancers occurring among participants who moved to those states during follow-up.

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; ref. 25), all primary incident cancers of the bronchus and lung (ICD 34.0–34.9) were considered for the present analysis. By histologic code, lung carcinomas included small cell (8002, 8041, 8042, 8043, 8044, and 8045), adenocarcinoma (bronchoalveolar: 8250, 8251, 8252, 8253, 8254 and other: 8140, 8255, 8260, 8310, 8323, 8480, 8481, 8490, 8550, and 8574), squamous cell (8050, 8070, 8071, 8072, 8073, 8074, and 8075), undifferentiated/large cell (8012, 8020, 8021, 8022, 8031, and 8032), and other or not otherwise specified (NOS) carcinoma (8010, 8011, 8033, 8046, and 8560).

Analytic population

We excluded 23,957 women who reported a history of cancer other than nonmelanoma skin cancer on the baseline questionnaire (including 46 lung cancers), 7,352 who were missing information on cigarette smoking, 1,651 with outliers for caloric intake, 7,021 premenopausal women, 6 with no follow-up, and 464 without evidence of having developed carcinomas [191 with only death certificate diagnoses, 126 neoplasms NOS, 72 carcinoid neoplasms, 59 neuroendocrine tumors, 7 sarcomas, 2 mesotheliomas, 7 *in situ* cancers]. Analyses therefore focused on 185,017 women.

Study entry and follow-up began at the date at which the baseline questionnaire was 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 3,512 women developed lung carcinomas.

Statistical analysis

We used Cox proportional hazards regression (using SAS 9.1.3 software, SAS Institute, Inc.), with age as the time scale and ties handled by complete enumeration (26), to estimate the relative risks (RR) and 95% CI of developing lung cancer. Tests of the proportional hazards assumptions for exposures and other variables included in statistical models revealed no departures. Tests for linear trends across the known exposure categories were

calculated by treating these categorical variables as ordinal variables. To test for heterogeneity in risk factor associations by histologic subtypes, we conducted case-only analyses using polytomous logistic regression adjusting for the same covariates included in our multivariate proportional hazards models as well as age at diagnosis to account for duration in the cohort.

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 compared with estimates from models adjusted only for age at entry. Our statistical models adjusted for age at entry, race/ethnicity, years of education, body mass index (BMI), history of emphysema, smoking status and dose, age at menarche, and type and age at menopause (including oophorectomy status). Adjustment for additional risk factors—including 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.

Results

Characteristics of the cohort

A total of 185,017 women contributed 1,816,356 person-years. The median ages at entry for lung cancer cases and non-diseased subjects were 62.6 and 64.4 years, respectively. The mean durations of follow-up (and upper range) were 5.7 years (11.1) for those who developed lung cancer ($n = 3,512$) and 9.9 (11.2) for those who did not.

Most women in the cohort were white, postmenopausal, and in their 60s when they completed the baseline questionnaire (Table 1). White women were slightly overrepresented in the lung cancer group (92.4%) versus the noncases (89.6%). 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.

Age-adjusted analyses showed a significant inverse relationship of lung cancer risk with age at menarche that persisted after adjustment for other factors, including cigarette smoking (RR = 0.84, 95% CI = 0.71–0.99 for 15+ vs. <11, $P_{trend} = 0.01$; Table 2). There was no significant relationship with either parity or number of births, but there was evidence of an inverse relationship with ages at first birth among parous women. This relationship became attenuated after adjustment for other risk factors, although the trend remained statistically significant at $P = 0.03$. We also examined relationships with use of oral contraceptives but saw no significant relationship with risk, even when long durations were considered.

When we examined a variety of menopausal factors, we found that age at natural menopause was significantly inversely related to risk (Table 3). Although the association became attenuated after adjustment, with the primary confounding factor being cigarette smoking, age at natural menopause remained a significant risk predictor (RR = 1.29, 95% CI = 1.14–1.46 for <45 vs. 50–54 years, used as a reference given that this represents the age range at which women normally experience natural menopause, $P_{trend} < 0.0001$). Women whose menstrual periods ceased as a result of a bilateral oophorectomy at a young age were also at an increased risk relative to those with a natural menopause at ages 50 to 54. These risks also became attenuated after adjustment for other risk factors, but women with a bilateral oophorectomy prior to the age of 40 remained at a significantly elevated risk (RR = 1.31, 95% CI = 1.15–1.50) compared with those with a natural menopause at 50 to 54 years (P_{trend} across oophorectomy ages = 0.01). In contrast to the relationships observed with ages at natural menopause or bilateral oophorectomy, after adjustment for other risk factors, there were no significant trends for ages at hysterectomy not involving removal of both ovaries.

Menopausal hormone users, particularly current users, were initially found to be at somewhat reduced risks compared with nonusers, but after adjustment for other factors (including type and age at menopause), the association was no longer apparent. After adjustment for other factors, we also observed no significant relationships with years of hormone use, even when analyses were restricted to current users or when we considered the type of menopause that women experienced (data not shown).

Smokers have previously been found to have earlier ages at natural menopause than nonsmokers (27) and we confirmed this relationship in our data. For instance, 9.7% of current long-term smokers had a natural menopause prior to age 45, as compared with only 5.8% of nonsmokers. As we were concerned that our results might reflect residual confounding by smoking, we examined reproductive and hormonal relationships stratified by smoking status; 276 lung cancer cases developed among never smokers (Table 4). The only factor that showed a significant relationship among never smokers was age at menarche (RR = 0.55, 95% CI = 0.30–1.00 for 15+ vs. <11, $P_{trend} = 0.03$). This exposure was less strongly related to risk among smokers, although both former and current smokers showed slight inverse trends. Age at first live birth was inversely related to risk across all smoking categories, but the trend was significant only among current smokers, where there was only minimal variation in risks across the categories. There was no evidence of any inverse relationship of either age at natural menopause or bilateral oophorectomy to risk among never smokers; however, former smokers showed significant inverse relationships with both types of menopause (respective trends of $P < 0.0001$ and $P < 0.001$), whereas current smokers showed a significant inverse trend with age at

Table 1. Risk factors for lung cancer among 185,017 women, NIH-AARP Diet and Health Study, 1995–2006

	n	
	Nondiseased subjects	**Lung cancer cases**
Number of study subjects	181,505	3,512
Person-years	1,796,451	19,905
Age at study entry, median (IQR)	62.58 (8.53)	64.44 (7.08)
Race/ethnicity, % Caucasian	162,597 (89.58)	3,245 (92.40)
Education, % post–high school training	117,859 (64.93)	2,020 (57.51)
Marital status, % currently married	80,451 (44.32)	1,221 (34.77)
BMI, median (IQR)	25.77 (6.67)	24.98 (6.02)
Emphysema, % with prior diagnosis	4,070 (2.24)	341 (9.71)
Currency and intensity of smoking, %		
Never	83,986 (46.27)	276 (7.86)
Former, ≤20 cigarettes/d	49,836 (27.46)	731 (20.81)
Former, >20 cigarettes/d	22,090 (12.17)	778 (22.15)
Current, ≤20 cigarettes/d	18,807 (10.36)	1,081 (30.78)
Current, >20 cigarettes/d	6,785 (3.74)	646 (18.39)
Alcohol intake, %		
0 drinks/d	54,327 (29.93)	943 (26.85)
>0–1 drink/d	104,086 (57.35)	1,867 (53.16)
>1–3 drinks/d	18,354 (10.11)	486 (13.84)
>3 drinks/d	4,735 (2.61)	216 (6.15)
Servings of fruit, per 1,000 kcal/d, median (IQR)	1.71 (1.51)	1.39 (1.40)
Serving of vegetables, per 1,000 kcal/d, median (IQR)	2.25 (1.47)	2.12 (1.45)
Red meat intake, g/1,000 kcal/d, median (IQR)	26.32 (24.35)	29.834 (25.76)
Processed meat intake, g/1,000 kcal/d, median (IQR)	5.72 (7.97)	6.35 (8.58)
Total daily energy intake, kcal, median (IQR)	1,457.49 (769.45)	1,453.01 (836.39)
Vigorous physical activity 5+ times/wk, %	29,494 (16.25)	435 (12.39)
Usual activity throughout the day, sitting all day, %	14,812 (8.16)	306 (8.71)

Abbreviation: IQR, interquartile range.

natural menopause ($P < 0.01$). Other factors, including parity and hormone use, did not show distinctive relationships within the smoking categories.

We further examined relationships by histologic subgroups (Table 5). We saw no statistically significant heterogeneity by histology for parity, age at first live birth or hormone use, but we did observe a significant inverse trend of later ages at menarche with adenocarcinomas (RR = 0.72. 95% CI = 0.56–0.93 for 15+ vs. <11; $P_{trend} < 0.01$). In contrast, age at menarche showed the opposite relationship with undifferentiated/large-cell tumors, namely a significant direct association ($P_{trend} = 0.02$). Age at natural menopause showed significant inverse relationships for both adenocarcinomas ($P_{trend} < 0.01$) and squamous cell carcinomas ($P_{trend} < 0.001$). Subjects with early bilateral oophorectomies (<40 years of age) were at an increased risk of developing adenocarcinomas (RR = 1.47, 95% CI = 1.21–1.79) as well as squamous cell cancers (RR = 1.53, 95% CI = 1.09–2.15), compared with women with natural menopause at ages 50 to 54 years.

When we examined smoking-stratified risks for adenocarcinomas, the only histologic subtype that allowed such detailed analyses (Table 6), we observed inverse trends of age at menarche across all smoking subgroups, although it was statistically significant only among current smokers. Coincidentally, the inverse relationship was also observed across all adult BMI subgroups (data not shown), a factor that has also been related to age at menarche.

In contrast to consistent patterns across smoking and BMI categories for age at menarche, the inverse relationship with age at natural menopause with adenocarcinomas predominated among former smokers, although was also present, albeit to a lesser extent, among never smokers. The inverse association with bilateral oophorectomy, however, was restricted to former smokers, with an opposite relationship seen among never smokers, based on small numbers.

Similar subgroup analyses for relationships with ages at menarche and menopause were not pursued for the squamous cell cancers given the small numbers of never-smokers who developed such cancers ($n = 14$).

Table 2. Associations between reproductive factors and lung cancer among 185,017 women, NIH-AARP Diet and Health Study, 1995–2006

Characteristic	*N* = 185,017	Person-years	No. of lung cancers (*n* = 3,512)	Age-adjusted RR[a]	95% CI	Multivariate RR[b]	95% CI
Age at menarche, y							
<11	12,490	121,546	250	1.00	Referent	1.00	Referent
11–12	77,613	762,065	1,491	0.90	0.78–1.02	0.91	0.80–1.04
13–14	76,778	754,596	1,423	0.84	0.74–0.96	0.86	0.75–0.98
15+	17,286	169,985	331	0.86	0.73–1.02	0.84	0.71–0.99
Missing	850	8,156	17	0.89	0.54–1.45	1.04	0.63–1.72
P_{trend}				0.03		0.01	
Parity							
Nulliparous	25,940	254,920	441	0.93	0.84–1.03	0.94	0.85–1.04
Parous	156,561	1,537,027	3,013	1.00	Referent	1.00	Referent
Missing	2,516	24,401	58	1.21	0.94–1.57	1.28	0.98–1.67
Number of births							
Nulliparous	25,940	254,920	441	1.00	Referent	1.00	Referent
1	18,942	185,251	403	1.26	1.10–1.44	1.13	0.98–1.29
2	47,387	467,933	804	0.98	0.88–1.10	0.99	0.88–1.12
3 or 4	68,838	676,078	1,349	1.08	0.97–1.20	1.07	0.96–1.20
5 or more	21,394	207,766	457	1.13	0.99–1.29	1.12	0.98–1.28
Missing	2,516	24,401	58	1.31	1.00–1.72	1.36	1.03–1.80
P_{trend}				0.38		0.20	
Age at first live birth among parous women, y							
<20	32,762	317,862	765	1.00	Referent	1.00	Referent
20–24	80,982	795,808	1,565	0.88	0.81–0.95	1.00	0.92–1.08
25–29	32,635	322,655	546	0.74	0.67–0.82	0.96	0.87–1.07
30+	10,603	104,813	154	0.64	0.54–0.76	0.87	0.74–1.04
Missing	2,095	20,290	41	0.90	0.66–1.22	1.08	0.78–1.49
P_{trend}				<0.0001		0.03	
Oral contraceptive use							
Never used/use <1 year	112,124	1,098,783	2,237	1.00	Referent	1.00	Referent
Use ≥1 year	71,256	701,634	1,241	1.07	0.99–1.15	1.04	0.97–1.12
Missing	1,637	15,932	34	1.09	0.78–1.53	1.21	0.84–1.74
Years of use of oral contraceptives							
Never used/use <1 year	81,347	793,009	1,715	1.00	Referent	1.00	Referent
1–4 years	35,310	349,033	561	1.04	0.95–1.15	1.01	0.92–1.12
5–9 years	25,088	249,257	364	1.09	0.98–1.22	1.06	0.95–1.19
10+ years	39,499	388,348	776	1.07	0.95–1.21	1.06	0.94–1.20
Missing	3,773	36,702	96	1.09	0.78–1.53	1.21	0.84–1.74
P_{trend}				0.09		0.21	

[a]RRs and 95% CIs from Cox models adjusted for age at entry into cohort.
[b]RRs and 95% CIs from Cox models adjusted for age at entry into cohort, race/ethnicity, education, BMI, emphysema, smoking status and dose, age at menarche, and type of and age at menopause.

Discussion

Evaluating the relationship of reproductive and hormonal factors to cancer risk is complicated given the high degree of correlation of these exposures. For lung cancer, the assessment is even more complex, given potential confounding by such risk factors as smoking and BMI (which is inversely related to risk). In the largest prospective study to date, we found some evidence, after controlling for pertinent factors (including cigarette smoking), that early menarche is associated with increases in the risk of adenocarcinomas. Early menopause also appeared to confer an increased risk of adenocarcinomas and squamous cell cancers, although primarily among smokers.

Table 3. Associations between menopausal factors and lung cancer among 185,017 women, NIH-AARP Diet and Health Study, 1995–2006

Characteristic	*N* = 185,017	Person-years	No. of lung cancers (*n* = 3,512)	Age-adjusted RR[a]	95% CI	Multivariate RR[b]	95% CI
Age at natural menopause, y							
<45	12,892	124,289	372	1.80	1.59–2.04	1.29	1.14–1.46
45–49	29,948	292,997	641	1.38	1.24–1.53	1.12	1.01–1.24
50–54	51,647	510,483	817	1.00	Referent	1.00	Referent
55+	11,543	114,063	162	0.82	0.69–0.97	0.98	0.82–1.16
P_{trend}[c]				<0.0001		<0.0001	
Age at surgical menopause, bilateral oophorectomy, y							
<40	12,344	119,546	317	1.74	1.53–1.98	1.31	1.15–1.50
40–44	9,409	92,357	198	1.33	1.14–1.55	1.18	1.01–1.38
45–49	9,718	96,049	160	1.05	0.89–1.25	1.07	0.90–1.26
50+	5,981	59,403	85	0.88	0.70–1.10	1.05	0.84–1.31
P_{trend}[c]				<0.0001		0.01	
Age at surgical menopause, both ovaries intact, y							
<40	14,111	137,963	254	1.25	1.09–1.44	1.12	0.97–1.29
40–44	7,686	75,400	154	1.26	1.06–1.49	1.20	1.01–1.43
45+	6,639	65,248	105	0.97	0.79–1.18	1.04	0.85–1.28
P_{trend}[c]				0.04		0.71	
Unknown type of menopause	7,693	75,240	167	1.40	1.19–1.65	1.24	1.05–1.46
Unknown age at menopause	5,406	53,310	80	0.97	0.77–1.22	0.97	0.76–1.23
Menopausal hormone use							
Never used	84,862	827,111	1,808	1.00	Referent	1.00	Referent
Current user	82,562	817,358	1,362	0.84	0.78–0.90	0.94	0.87–1.02
Former user	17,150	167,481	336	0.93	0.83–1.04	0.92	0.82–1.04
Missing	443	4,398	6	0.64	0.29–1.43	0.64	0.29–1.44
Years of use of menopausal hormones							
Never used	81,347	793,009	1,715	1.00	Referent	1.00	Referent
<5	35,310	349,033	561	0.86	0.78–0.95	0.96	0.87–1.06
5–9	25,088	249,257	364	0.77	0.69–0.86	0.92	0.82–1.04
10+	39,499	388,348	776	0.92	0.84–1.00	0.95	0.87–1.05
Missing	3,773	36,702	96	1.20	0.98–1.48	1.27	1.03–1.57
P_{trend}				<0.01		0.21	

[a]RRs and 95% CIs from Cox models adjusted for age at entry into cohort.

[b]RRs and 95% CIs from Cox models adjusted for age at entry into cohort, race/ethnicity, education, BMI, emphysema, age at menarche, and smoking status and dose.

[c]Trends were calculated within menopause subgroups, using the youngest age as the referent, despite the use of a different referent group for the calculation of RRs.

Although relationships with menstrual factors were somewhat provocative, we found limited support for a role of other reproductive factors in the etiology of lung cancers. The factor that has received the most attention in previous studies has been parity, which has been related to decreased risk in a number of investigations (4–7, 28), although other studies have found either increased risk related to this exposure (8, 29) or no apparent effect (9–12, 20, 30–33). Given that parity is strongly influenced by many factors, including cigarette smoking and social class, the relationships in some of these studies may have reflected uncontrolled confounding or biased control selection. It is noteworthy that we did not observe any evidence of a relationship even prior to adjustment for other factors, which may reflect that our population was composed of generally middle to upper social class subjects, possibly obviating the positive confounding by social class that may have affected some previous studies.

Table 4. Associations between selected reproductive and menopausal risk factors and lung cancer by smoking status among 185,017 women, NIH-AARP diet and health study, 1995–2006

Characteristic	Lung cancers ($n = 276$)	Never smokers		Lung cancers ($n = 1,509$)	Former smokers		Lung cancers ($n = 1,727$)	Current smokers	
		RR[a]	95% CI		RR[a]	95% CI		RR[a]	95% CI
Age at menarche, y									
<11	23	1.00	Referent	99	1.00	Referent	128	1.00	Referent
11–12	121	0.76	0.48–1.19	639	0.94	0.76–1.17	731	0.92	0.76–1.11
13–14	109	0.66	0.42–1.04	620	0.89	0.72–1.10	694	0.87	0.72–1.05
15+	21	0.55	0.30–1.00	143	0.91	0.70–1.18	167	0.84	0.67–1.06
Missing	2	0.95	0.21–4.29	8	1.15	0.55–2.42	7	0.95	0.44–2.09
P_{trend}		0.03			0.26			0.08	
Age at first live birth among parous women, y									
<20	38	1.00	Referent	295	1.00	Referent	432	1.00	Referent
20–24	126	0.98	0.74–1.30	677	0.99	0.88–1.12	762	0.97	0.87–1.08
25–29	53	0.90	0.63–1.28	266	1.00	0.86–1.17	227	0.87	0.74–1.01
30+	10	0.51	0.26–0.99	69	0.83	0.64–1.07	75	0.96	0.75–1.22
Missing	2	0.49	0.12–2.08	20	1.25	0.78–2.00	19	1.02	0.64–1.63
P_{trend}		0.22			0.18			0.04	
Type of and age at menopause									
Natural menopause, y									
<45	17	1.01	0.60–1.72	143	1.37	1.13–1.67	212	1.29	1.09–1.52
45–49	34	0.87	0.58–1.30	270	1.20	1.02–1.40	337	1.12	0.96–1.29
50–54	78	1.00	Referent	362	1.00	Referent	377	1.00	Referent
55+	23	1.11	0.70–1.77	76	0.89	0.69–1.14	63	1.00	0.77–1.31
P_{trend}[b]		0.56			<0.0001			<0.01	
Surgical menopause, bilateral oophorectomy, y									
<40	14	0.94	0.53–1.67	146	1.64	1.35–2.00	157	1.18	0.98–1.42
40–44	13	0.96	0.53–1.73	95	1.36	1.08–1.70	90	1.09	0.86–1.37
45–49	19	1.30	0.79–2.15	71	1.04	0.81–1.34	70	1.05	0.81–1.35
50+	14	1.39	0.79–2.46	42	1.02	0.74–1.40	29	0.92	0.63–1.35
P_{trend}[b]		0.21			<0.001			0.18	

[a]RRs and 95% CIs from Cox models adjusted for age at entry into cohort, race/ethnicity, education, BMI, emphysema, smoking status and dose, age at menarche, and type and age at menopause.

[b]Trends were calculated within menopause subgroups, using the youngest age as the referent, despite the use of a different referent group for the calculation of the RRs.

Although several studies have found inverse associations with ages at first birth (9, 34), a greater number have failed to note any relationship (4, 5, 7, 11, 12, 20, 31). We initially observed an inverse relationship of risk with late ages at first birth, but this association was not particularly convincing after adjustment for other factors, including smoking, and we saw no significant relationships within any defined histologic subgroups. We also saw no association with use of oral contraceptives, in agreement with most prior investigations (7, 20, 29, 34, 35), but in contrast with several studies that have noted either reduced (9, 33) or increased (12) risks.

Many studies (9, 15–20), although not all (6, 8, 31–33, 36–38), have noted a reduced risk of lung cancer associated with use of menopausal hormones. In several, the reduced risks were strongest in smokers (16, 19). In contrast, our results showed little evidence that exogenous hormones reduced the risk of lung cancer; in fact, the slightly reduced risks initially observed disappeared after adjustment for smoking, in agreement with another recent study (4). We also did not observe reduced risks even when more detailed parameters of usage were considered (e.g., currency, years of use), nor did we see evidence when histology-specific relationships (including for adenocarcinomas) and smoking-stratified relationships were examined. However, due to the small number of cases among never smokers, it remains possible that we may have failed to detect weak associations for both hormone use and parity. We were also limited by the fact that our baseline questionnaire did not collect information on hormone formulations. Although one recent study noted an increased risk of lung cancer associated with use of estrogen plus progestin therapy (39), other investigations have not found significant risk

Table 5. Associations between selected reproductive and menopausal risk factors and lung cancer by histology among 185,017 women, NIH-AARP Diet and Health Study, 1995–2006

Characteristics	Small cell ($n = 578$)		Non–small cell carcinomas								
			Adenocarcinoma ($n = 1,520$)		Squamous cell ($n = 515$)		Non–small cell, NOS ($n = 408$)		Undifferentiated/large cell ($n = 81$)		
	RR[a]	(95% CI)	RR[a]	(95% CI)	RR[a]	(95% CI)	RR[a]	(95% CI)	RR[a]	(95% CI)	P[b]
Age at menarche, y											0.05
<11	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	
11–12	0.83	0.61–1.14	0.87	0.71–1.06	1.38	0.91–2.11	0.62	0.43–0.89	1.48	0.68–3.22	
13–14	0.75	0.54–1.03	0.78	0.64–0.95	1.41	0.92–2.15	0.71	0.50–1.02	1.68	0.77–3.66	
15+	0.76	0.51–1.12	0.72	0.56–0.93	1.14	0.69–1.88	0.69	0.44–1.09	2.31	1.00–5.35	
Missing	0.89	0.27–2.98	1.08	0.52–2.25	1.00	0.23–4.39	1.15	0.27–4.94	3.50	0.41–29.73	
P_{trend}	0.09		<0.01		0.90		0.78		0.02		
Age at first live birth among parous women, y											0.33
<20	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	
20–24	0.90	0.74–1.08	1.10	0.98–1.24	1.04	0.85–1.27	1.10	0.88–1.38	0.72	0.51–1.01	
25–29	1.08	0.84–1.39	1.08	0.93–1.27	0.87	0.66–1.17	0.73	0.52–1.02	0.82	0.53–1.29	
30+	0.83	0.54–1.29	0.84	0.64–1.09	0.91	0.58–1.43	1.22	0.79–1.88	0.83	0.41–1.67	
Missing	1.09	0.50–2.41	0.87	0.50–1.52	1.62	0.81–3.26	1.03	0.37–2.86	0.95	0.23–4.00	
P_{trend}	0.73		0.37		0.09		0.25		0.97		
Type of and age at menopause											0.76
Natural menopause, y											
<45	0.89	0.64–1.24	1.29	1.06–1.57	1.70	1.25–2.31	1.15	0.82–1.62	1.55	0.93–2.59	
45–49	1.12	0.88–1.44	1.17	1.00–1.37	1.33	1.01–1.74	0.84	0.62–1.14	1.12	0.71–1.77	
50–54	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	
55+	1.19	0.80–1.75	0.94	0.73–1.23	0.81	0.49–1.36	0.99	0.64–1.54	0.92	0.43–1.95	
P_{trend}[c]	0.50		<0.01		<0.001		0.83		0.10		
Surgical menopause, bilateral oophorectomy, y											
<40	1.16	0.84–1.60	1.47	1.21–1.79	1.53	1.09–2.15	1.12	0.77–1.62	1.27	0.70–2.30	
40–44	1.01	0.68–1.50	1.18	0.92–1.50	1.49	1.00–2.20	0.98	0.63–1.54	1.55	0.83–2.89	
45–49	0.77	0.48–1.24	1.16	0.90–1.49	1.07	0.67–1.72	0.81	0.49–1.35	1.32	0.66–2.63	
50+	0.91	0.50–1.64	1.27	0.93–1.73	1.08	0.58–2.01	0.44	0.18–1.07	0.73	0.23–2.35	
P_{trend}[c]	0.16		0.16		0.14		0.04		0.54		

NOTE: Subjects with carcinomas, NOS ($n = 311$) not included in analyses.

[a]RR and 95% CI from Cox models adjusted for age at entry into cohort, race/ethnicity, education, BMI, emphysema, smoking status and dose, age at menarche, and type of and age at menopause.

[b]P for heterogeneity obtained through polytomous regression where the dependent variable is categorized as small cell, adenocarcinoma, squamous cell, non–small cell (NOS), and undifferentiated/large cell. The reference category is adenocarcinoma.

[c]Trends were calculated within menopause subgroups, using the youngest age as the referent, despite the use of a different referent group for the calculation of the RRs.

Table 6. Associations between age at menarche and type of and age at menopause and adenocarcinoma, NIH-AARP Diet and Health Study, 1995–2006

	Never smokers			Former smokers			Current smokers		
Characteristics	**No. of cancers**	**RR[a]**	**95% CI**	**No. of cancers**	**RR[a]**	**95% CI**	**No. of cancers**	**RR[a]**	**95% CI**
Age at menarche, y									
<11	12	1.00	Referent	50	1.00	Referent	55	1.00	Referent
11–12	81	0.97	0.53–1.78	301	0.88	0.65–1.19	279	0.84	0.63–1.13
13–14	75	0.87	0.47–1.60	296	0.84	0.62–1.14	232	0.69	0.52–0.93
15+	13	0.67	0.30–1.47	55	0.71	0.48–1.04	62	0.75	0.52–1.08
Missing	0			4	1.24	0.43–3.54	4	1.28	0.44–3.69
P_{trend}		0.20			0.09			0.02	
Age at natural menopause, y									
<45	11	1.09	0.56–2.09	64	1.30	0.98–1.73	72	1.43	1.06–1.92
45–49	24	0.98	0.60–1.60	123	1.12	0.89–1.41	128	1.34	1.04–1.72
50–54	49	1.00	Referent	180	1.00	Referent	118	1.00	Referent
55+	11	0.86	0.45–1.65	28	0.66	0.45–0.99	29	1.50	1.00–2.25
P_{trend}[b]		0.66			<0.01			0.10	
Age at bilateral oophorectomy, y									
<40	8	0.90	0.43–1.91	71	1.69	1.28–2.23	62	1.49	1.09–2.02
40–44	10	1.22	0.62–2.42	43	1.29	0.92–1.80	27	1.06	0.69–1.60
45–49	15	1.66	0.93–2.97	35	1.04	0.72–1.50	23	1.11	0.71–1.73
50+	11	1.76	0.92–3.39	21	1.02	0.65–1.60	13	1.35	0.76–2.40
P_{trend}[b]		0.10			<0.01			0.35	

[a]RRs and 95% CIs from Cox models adjusted for age at entry into cohort, race/ethnicity, education, BMI, emphysema, smoking status and dose, and, as appropriate, age at menarche, age at natural menopause or age at bilateral oophorectomy.
[b]Trends were calculated within menopause subgroups, using the youngest age as the referent, despite the use of a different referent group for the calculation of the RRs.

differences for estrogens alone versus estrogens plus progestins (20–22, 40). However, analyses using later questionnaires administered to participants in our study will allow this issue to be examined in more detail.

Consistent with a few lung cancer investigations that have observed inverse relations with age at menarche (10, 11, 34), we noted a similar relationship for adenocarcinomas, the lung cancer subtype least influenced by cigarette smoking (41). The relationship could not be attributed to confounding by smoking (as it was evident in never smokers) or to obesity (as this was inversely associated with both age at menarche and lung cancer risk in our study). Although this may suggest that hormonal factors early in life are important initiating factors for subsequent lung pathologies, including adenocarcinomas, it should be noted that age at menarche can be influenced by many early life exposures that were not measured in our investigation. Chance must also be considered a possible explanation for the observed inverse relation with age at menarche. Nonetheless, it is of interest that asthma becomes more pronounced in girls at puberty (2) and that women with early menarche have lower lung function and more adult asthma (42), a factor that preferentially affects lung cancer risk in nonsmokers (43). Further clarity about the role of age at menarche on subsequent lung cancer risk would benefit from additional research that better defines its effect on cellular changes in the lung.

Somewhat contradictory to our findings about a potentially adverse impact of early ages at menarche on the risk of adenocarcinomas, we found that early ages at natural menopause appeared to increase the risk of both adenocarcinomas and squamous cell cancers, suggesting that continued production of hormones may exert some protection against the development of these cancers. Further supporting this concept were significantly elevated overall lung cancer risks among women in our study who had bilateral oophorectomies at early ages. In contrast, we observed no impact on risk of hysterectomies involving ovarian conservation, suggesting that premature cessation of ovarian function may play an adverse role in lung carcinogenesis.

Our findings are consistent with several previous investigations that have noted elevated lung cancer risks among women with bilateral oophorectomies (11, 14) as well as among those with young ages at natural menopause (7, 10–13, 31, 33). One of these

investigations (31) hypothesized that the relationship may reflect a tendency for women with early menstrual cessation to be prescribed hormones for extended periods, but this seems an unlikely explanation for our finding given the absence of any significant effect of hormone use. We also observed an inverse relationship with age at natural menopause even among non–hormone users.

Given earlier ages at menopause among smokers (27), the possibility of confounding by cigarette smoking deserves special consideration. Although our relationships were considerably attenuated after adjustment for smoking, we continued to observe significantly elevated risks among those with early menstrual cessation. The ultimate control for smoking, however, is to examine risks among nonsmokers. Although 2 previous studies, focused solely on nonsmoking women (7, 31), have noted reduced risks of lung cancer with late menstrual cessation, in our study among never smokers we saw no risk related to age at menopause overall and only a slight, albeit nonsignificant, inverse trend of age at natural menopause related to risk of adenocarcinomas. Thus, our findings about the effects of menstrual cessation on lung cancer risk must be cautiously interpreted.

Nonetheless, it has been suggested that hormonal factors might have stronger effects among smokers due to the strong binding of hormones to estrogen receptors in the lung, limiting the carcinogenic potential of polycyclic aromatic hydrocarbons, which also bind to these receptors (19). It is also possible that the restriction of age at menopause relationships to smokers, particularly current smokers, could imply an enhanced opportunity for effects among individuals with lowered endogenous estrogens (44). This effect modification would be analogous to stronger effects of exogenous hormones observed for breast and endometrial cancers risks among thin women (45, 46), who also have lowered levels of endogenous estrogens. Biological credibility for a beneficial role of estrogens in the pathogenesis of lung cancers also derives from findings that estradiol can uniquely interact with estrogen receptor β and inhibit transcriptional activities (47) and have negative feedback on aromatase, which is produced in normal lung tissue (3). In addition, estrogens have been shown to influence the cytokine milieu (48) and to be important in alveolar regeneration and control of extracellular matrix deposition (49), which may be important in preventing chronic inflammation and fibrosis. Thus, the hypothesis that menopausal age could affect lung cancer risk appears worthy of further pursuit in additional investigations.

Our study had a number of strengths over previous investigations, most of which have had to rely on recall for exposures given their case–control designs. The largest cohort studies have focused on 750 (8) and 1,729 (12) lung cancer cases. Our study had relatively complete information on most reproductive and hormonal risk factors hypothesized to play a role in the development of lung cancers in over 3,500 lung cancer cases. Although we had extensive information on most other important risk predictors, we were lacking data on passive smoking, but this is probably not a major confounding factor (50). Information on clinical characteristics of the tumors, available from cancer registries, coupled with large numbers, also allowed us to assess relationships according to subgroups defined by tumor histology.

Although the results of our study do not support the notion that most reproductive factors or exogenous hormones play a role in lung carcinogenesis, we did find some support for menstrual factors. The relationships were somewhat complex, and therefore will require confirmation in future investigations. Early ages at menarche appeared to be predictive of elevated adenocarcinoma risks, possibly supporting an adverse effect of estrogenic influences on tumor initiation. Although requiring cautious interpretation due to possible confounding by smoking, there was some evidence that continued hormonal production at late ages was protective of risk of both adenocarcinomas as well as squamous cell cancers, possibly reflecting beneficial effects in terms of cellular maintenance and immunologic responses. Additional studies addressing the biological mechanisms that might underlie hormonal risk factors in the etiology of lung cancer may be helpful in furthering our understanding of the pathogenesis of lung cancers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

This investigation was supported by the intramural research program of the NIH.

Received December 21, 2010; revised March 2, 2011; accepted March 14, 2011; published OnlineFirst April 5, 2011.

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