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Original Contribution

Menstrual and Reproductive Factors in Association With Lung Cancer in Female Lifetime Nonsmokers

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Cigarette smoking is irrefutably the strongest risk factor for lung cancer; however, approximately 25% of cases worldwide occur among nonsmokers. The age-adjusted annual incidence rate of lung cancer in Shanghai, a region where relatively few women smoke cigarettes, is one of the highest in the world. To help further elucidate the etiology of lung cancer among nonsmokers, the authors examined hormonal factors among women who were lifetime nonsmokers. They analyzed data from the prospective Shanghai Women's Health Study, which recruited Chinese women aged 40–70 years between 1996 and 2000 from selected urban communities. The current analysis included 71,314 women ($n = 220$ cases) who were lifetime nonsmokers and had no history of cancer at baseline. Later age at menopause ($\geq$51 vs. $<$46 years; hazard ratio (HR) = 0.63, 95% confidence interval (CI): 0.40, 1.00), longer reproductive period ($\geq$36 vs. $<$31 years; HR = 0.60, 95% CI: 0.39, 0.93), higher parity ($\geq$4 vs. 0 children; HR = 0.42, 95% CI: 0.19, 0.90), and intrauterine device use (HR = 0.59, 95% CI: 0.41, 0.86) were associated with decreased risks of lung cancer. This large prospective study suggests a potential role for hormonal factors in the etiology of lung cancer among nonsmoking women.

hormones; lung; menstrual cycle; neoplasms; parity

Abbreviations: CI, confidence interval; HR, hazard ratio.

Smoking is a strong risk factor for lung cancer, and 85%–90% of lung cancer deaths are attributable to cigarette smoking (1). The remaining 10%–15% occur among nonsmokers, so other factors are likely involved in the etiology of this disease. Candidate contributors include secondhand smoke exposure, air pollution, occupational exposures (e.g., arsenic, asbestos, radon, tar, chromium), cooking practices (e.g., use of solid fuels and high-temperature frying), family history of cancer, prior lung disease, and dietary components, as shown by review (2). Among female nonsmokers, reproductive and hormonal exposures have also been proposed to play a role (3, 4), but these variables have not been well studied, and thus a role for these factors has not been clearly established.

Estrogen could influence cancer development through direct promotion of cellular proliferation in the lung. Estrogen metabolites could also induce direct DNA damage (5). Indirectly, hormones could act through their influence on the expression of genes involved in carcinogen metabolism or via regulation of cytokine or growth factor secretion that determine how the lungs respond to irritants (6). The biologic plausibility of hormonal involvement in lung carcinogenesis is supported by studies that have identified sex hormone receptors (estrogen and progesterone) in lung cancer cell lines and tumor tissues (7–10). Few epidemiologic studies, however, have examined hormonal and reproductive risk factors for lung cancer, and the findings have not been consistent (11–22).

Lung cancer incidence and mortality rates among men have dropped over the last decade, but not among women. The death rate in females has increased 600% since 1950 in the United States (23). Differences in incidence and mortality between the sexes could reflect differences in susceptibility to disease and disease progression, but this notion is

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controversial (24–28). The most recent analysis of 2 large American Cancer Society Prevention Study cohorts (CPS-I and CPS-II) did not observe sex differences in lung cancer mortality among nonsmokers (27). It has been estimated, however, that anywhere from 3% to 15% of men and from 33% to 53% of all women with lung cancer worldwide are never smokers (6, 29). It is unclear whether the higher incidence among female nonsmokers is due to differences in exposure or susceptibility between men and women. Adenocarcinoma of the lung, shown to have a weaker association with tobacco smoking than other histologic types of lung cancer, is also observed predominantly in women, suggesting a possible role for female hormones in this form of the disease (30, 31). To help further elucidate the etiology of lung cancer among nonsmokers, we examined hormonal factors among women who were lifetime nonsmokers.

MATERIALS AND METHODS

The Shanghai Women's Health Study

From 1996 to 2000, 74,942 Chinese women aged 40–70 years were recruited to participate in the prospective Shanghai Women's Health Study. The cohort, enrollment, and follow-up have previously been described in detail (32). In brief, the study was conducted in 7 urban communities in Shanghai, with rosters of all eligible women who lived in these communities obtained from the resident offices. The incidence rates of major cancers, as well as the distributions of age, sex, educational level, and occupation of the study population, were similar to those of the entire population of urban Shanghai (32). Of 81,170 eligible women who lived in the study communities during the time period of the baseline survey, 75,221 (92.7%) participated in the study. Between 2001 and 2004, 74,942 (99.6%) of these women completed the first follow-up survey. The cohort has been followed for mortality and cancer incidence by using a combination of record linkage and active follow-up. Interviewers visit each participant every 2 years to update health history and lifestyle factors. Cancer diagnoses and deaths are verified through medical chart review.

Study population

We excluded women with a history of cancer at study entry ($n = 1{,}576$) and those missing information on the date at first follow-up ($n = 8$). Of the remaining 73,358 eligible women, 71,314 (97%) were lifetime nonsmokers and were included in the current analysis. Incident cases ($n = 220$) were diagnosed between 1996 and December 2005 with malignant neoplasm of the bronchus or lung (*International Classification of Diseases*, Ninth Revision, codes 162.0–162.9).

Baseline exposure assessment

All participants completed a 2-part questionnaire at study enrollment. Part 1 of the questionnaire was self-administered, and part 2 was interview administered. Study participants completed the self-administered questionnaire that included questions on demographics, current and past smoking behavior, medical history and medication use, menstrual history, family history of cancer, occupational history, and spousal information (including smoking). Interviewers then reviewed the completeness and accuracy of the self-administered questionnaires and administered the second part of the baseline survey. Information was collected on dietary habits, reproductive history and hormone use, passive smoke exposure at home and at work, physical activity over the past 5 years and during adolescence, and weight and height history. Interviewers obtained anthropometric measurements and collected blood and urine samples. With respect to passive smoke exposure, information was collected at baseline for exposures through the husband and at the workplace. Information on smoking in the home before and after the age of 20 years (years, cigarettes per day, hours per day) was obtained at first follow-up, which took place approximately 2 years after baseline for most participants.

Statistical analyses

The association between various hormonal factors and risk of lung cancer was evaluated by using Cox proportional hazards with age as the time scale and stratification by birth cohort (5-year intervals). Exposure variables included menopausal status (premenopausal, postmenopausal), age at menarche (<15, 15–16, ≥ 17 years), age at menopause (<46, 46–48, 49–50, ≥ 51 years), reproductive period (<31, 31–33, 34–35, ≥ 36 years), parity (0, 1–3, ≥ 4 births), age at first birth (<23, 23–25, 26–27, ≥ 28 years), intrauterine device use (never/ever), oral contraceptive use (never/ever), and postmenopausal hormone use (never/ever). Change in menopausal status after baseline was accounted for by splitting the follow-up time at the date of menopause. The reproductive period was calculated as the years between menarche and menopause.

The factors evaluated as potential confounders included age, education, marital status, income, body mass index, family history of cancer, history of respiratory disease, passive smoke exposure, alcohol consumption, cooking fuel/oil, nutritional factors, and the exposure variables. Passive smoke exposure was defined as ever exposure in the home or workplace. Nutritional factors were modeled as categorical variables defined by the quartile distributions among controls. Covariates were evaluated as potential confounders by assessing whether their inclusion altered risk estimates by $>10\%$.

The risk of lung cancer associated with age at menarche and age at menopause was also modeled with stratification by passive smoke exposure. To test for linear trends in hazard ratios across groups, we created score variables representing the median of each category and included them into the Cox models as continuous variables. For dichotomous variables, Wald's P values indicate the significance of trend between the respective levels. Likelihood ratio tests were performed to test for multiplicative interactions. All analyses were performed by using the STATA 9.0 statistical package (StataCorp LP, College Station, Texas).

RESULTS

A total of 506,522 person-years were accrued in this population of female lifetime nonsmokers. Cases were followed for an average of 4.1 years from study entry to diagnosis. Cases were significantly older than the cohort but were similar with respect to educational level, marital status, family history of cancer, alcohol consumption, and adult exposure to passive smoke (Table 1). Although excluded from analyses, ever smokers had a 2-fold increased risk of lung cancer (hazard ratio (HR) = 2.38, 95% confidence interval (CI): 1.54, 3.68; results not shown).

A later age at menarche (≥17 vs. <15 years; HR = 1.38, 95% CI: 0.94, 2.04) was associated with a nonsignificantly increased risk of lung cancer (Table 2). Decreased risk was observed among women with a later age at menopause (≥51 vs. <46 years; HR = 0.63, 95% CI: 0.40, 1.00; P_{trend} = 0.03), longer reproductive period (years between menarche and menopause, ≥36 vs. <31 years; HR = 0.60, 95% CI: 0.39, 0.93; $P_{trend} < 0.01$), higher parity (≥4 vs. 0 children; HR = 0.42, 95% CI: 0.19, 0.90; $P_{trend} < 0.01$), and intrauterine device use (HR = 0.59, 95% CI: 0.41, 0.86; P_{trend} = 0.01). Lung cancer risk was not associated with menopausal status, age at first birth, use of oral contraceptives, or use of postmenopausal hormone therapy. Similar results and trends were observed when analyses were restricted to women with natural menopause (results not shown).

Of 220 diagnosed cases, data on histologic types were available for 168 cases (76%). Of the cases with histologic confirmation, 78 women were diagnosed with adenocarcinoma of

Table 1. Associations of Lung Cancer Diagnosed Between 1996 and 2005 and Selected Risk Factors Among Female Nonsmokers, Shanghai Women's Health Study

Characteristic	No. of Cancers (*N* = 220)	Person-Years (Total = 506,522)	Hazard Ratio[a]	95% Confidence Interval	P_{trend}
Age, years[b]					
40–44	19	145,655	1.00	Referent	
45–49	30	107,416	2.04	1.13, 3.72	
50–54	25	72,845	2.46	1.32, 4.58	
55–59	30	51,871	4.59	2.55, 8.29	
60–64	45	63,586	5.28	3.02, 9.23	
≥65	71	65,147	7.50	4.39, 12.82	<0.01
Education					
College/more	30	71,816	1.00	Referent	
High school	42	143,762	0.90	0.54, 1.50	
Middle school	64	189,685	1.04	0.64, 1.69	
Elementary/less	84	101,197	1.07	0.66, 1.76	0.56
Marital status					
Never married	0	4,405			
Currently married	183	452,872	1.00	Referent	
Widowed, separated, divorced	37	49,244	1.27	0.81, 1.98	0.30
Family history of cancer					
No	159	377,783	1.00	Referent	
Yes	61	128,739	1.14	0.83, 1.56	0.42
Family history of lung cancer					
No	211	481,744	1.00	Referent	
Yes	9	24,777	0.90	0.44, 1.82	0.76
Alcohol consumption					
Never	218	496,620	1.00	Referent	
Ever	2	9,902	0.49	0.12, 1.98	0.32
Passive smoke exposure					
Never	43	77,657	1.00	Referent	
Ever	155	407,733	0.94	0.65, 1.35	0.72

[a] Hazard ratios adjusted for passive smoke exposure (never/ever); passive smoke exposure is defined as ever exposure in the home or workplace. Unknown educational level: 0 cases, 62 person-years; unknown passive smoke exposure: 22 cases, 21,132 person-years.

[b] Time on study = timescale for analysis of age as the main effect.

Table 2. Associations of Lung Cancer Diagnosed Between 1996 and 2005 and Menstrual and Reproductive Factors Among Female Nonsmokers, Shanghai Women's Health Study

Characteristic	No. of Cancers	Person-Years	Hazard Ratio[a]	95% Confidence Interval	Hazard Ratio[b]	95% Confidence Interval	Hazard Ratio[c]	95% Confidence Interval	P_{trend}[d]
Menopausal status									
Premenopausal	40	222,758	1.00	Referent	1.00	Referent	1.00	Referent	
Postmenopausal	180	283,764	1.22	0.68, 2.19	1.24	0.67, 2.30	1.35	0.50, 3.65	0.49
Age at menarche, years									
<15	74	218,751	1.00	Referent	1.00	Referent	1.00	Referent	
15–16	87	199,650	1.12	0.82, 1.54	1.23	0.88, 1.72	1.10	0.63, 1.92	
≥17	59	87,982	1.40	0.98, 1.98	1.38	0.94, 2.04	1.24	0.65, 2.37	0.09
Age at menopause, years									
<46	54	74,726	1.00	Referent	1.00	Referent	1.00	Referent	
46–48	52	91,885	0.69	0.47, 1.01	0.60	0.40, 0.90	0.46	0.24, 0.88	
49–50	36	61,461	0.72	0.47, 1.10	0.64	0.40, 1.00	0.43	0.20, 0.92	
≥51	38	55,692	0.79	0.51, 1.20	0.63	0.40, 1.00	0.36	0.16, 0.82	0.03
Reproductive period, crude, years[e]									
<31	71	85,824	1.00	Referent	1.00	Referent	1.00	Referent	
31–33	43	81,724	0.61	0.42, 0.90	0.57	0.38, 0.85	0.38	0.19, 0.77	
34–35	26	53,775	0.57	0.36, 0.90	0.48	0.29, 0.79	0.45	0.21, 0.96	
≥36	40	62,406	0.73	0.49, 1.09	0.60	0.39, 0.93	0.33	0.15, 0.74	<0.01
Parity (no. of livebirths)									
0	10	16,453	1.00	Referent	1.00	Referent	1.00	Referent	
1–3	177	441,997	0.79	0.41, 1.49	0.74	0.38, 1.46	1.18	0.29, 4.84	
≥4	33	48,072	0.45	0.22, 0.93	0.42	0.19, 0.90	0.84	0.18, 3.96	<0.01
Age at first birth, years									
<23	88	123,183	1.00	Referent	1.00	Referent	1.00	Referent	
23–25	44	136,628	0.85	0.58, 1.24	0.84	0.55, 1.26	0.65	0.32, 1.29	
26–27	39	108,041	1.26	0.83, 1.91	1.32	0.84, 2.06	1.09	0.53, 2.25	
≥28	39	122,204	1.04	0.69, 1.59	1.15	0.74, 1.79	0.57	0.25, 1.31	0.43
Intrauterine device use									
Never	150	223,955	1.00	Referent	1.00	Referent	1.00	Referent	
Ever	70	282,567	0.78	0.55, 1.11	0.59	0.41, 0.86	0.52	0.28, 0.98	0.01
Oral contraceptive use									
Never	174	402,589	1.00	Referent	1.00	Referent	1.00	Referent	
Ever	46	103,933	0.99	0.71, 1.38	0.98	0.69, 1.40	0.98	0.54, 1.76	0.93
Hormone replacement therapy use									
Never	216	488,430	1.00	Referent	1.00	Referent	1.00	Referent	
Ever	4	18,091	0.60	0.22, 1.61	0.50	0.16, 1.56			0.23

[a] Unadjusted hazard ratios. Unknown menopausal status: 0 cases, 87 person-years; unknown age at menarche: 0 cases, 138 person-years; unknown age at menopause: 40 cases, 222,758 person-years; unknown reproductive years: 40 cases, 222,792 person-years; unknown age at first birth: 10 cases, 16,466 person-years.

[b] Hazard ratios adjusted for passive smoke exposure (yes/no). Unknown passive smoke exposure: 22 cases, 21,132 person-years.

[c] Known adenocarcinoma cases only ($n = 78$).

[d] P_{trend} for analyses of all cases.

[e] Crude reproductive period = age at menopause − age at menarche.

the lung. Similar, even slightly more pronounced, associations were observed in women diagnosed with adenocarcinoma compared with all histologic subtypes combined (Table 2).

Risk estimates were comparable when analyses were stratified by passive smoke exposure, with multiplicative tests for interaction not significant ($P > 0.05$; Table 3).

Table 3. Associations of Lung Cancer Diagnosed Between 1996 and 2005 and Ages at Menarche and Menopause Stratified by Exposure to Passive Smoke,[a] Shanghai Women's Health Study

Characteristic	No Passive Smoke Exposure					Passive Smoke Exposure				
	No. of Cancers	Person-Years	Hazard Ratio	95% Confidence Interval	P_{trend}	No. of Cancers	Person-years	Hazard Ratio	95% Confidence Interval	P_{trend}
Age at menarche, years										
<15	14	31,586	1.00	Referent		51	177,188	1.00	Referent	
15–16	16	30,488	1.00	0.46, 2.17		66	161,121	1.29	0.89, 1.86	
≥17	13	15,558	1.19	0.50, 2.82	0.70	38	69,319	1.43	0.93, 2.19	0.09
Age at menopause, years										
<45	13	13,378	1.00	Referent		39	52,428	1.00	Referent	
46–48	11	17,631	0.68	0.29, 1.57		29	60,115	0.57	0.36, 0.92	
49–50	8	11,435	0.49	0.17, 1.41		23	39,102	0.68	0.41, 1.12	
≥51	7	10,622	0.69	0.26, 1.79	0.31	19	33,884	0.62	0.37, 1.05	0.06
Reproductive period, crude, years										
<31	16	16,363	1.00	Referent		49	60,280	1.00	Referent	
31–32	7	9,723	0.57	0.24, 1.36		18	34,095	0.57	0.36, 0.90	
33–35	8	15,686	0.44	0.14, 1.36		24	52,114	0.49	0.28, 0.86	
≥36	8	11,275	0.78	0.32, 1.90	0.37	19	39,032	0.56	0.34, 0.93	<0.01

[a] Passive smoke exposure is defined as ever exposure in the home or workplace; missing information on passive smoke exposure: 22 cases, 21,132 person-years.

DISCUSSION

In our study, the risk of lung cancer among female lifetime nonsmokers was decreased among those with increased parity, later age at menopause, and longer length of reproductive years. The decreased risk associated with a longer reproductive period was similar, or slightly more pronounced, among women with adenocarcinoma of the lung.

A role for female sex hormones in the etiology of lung cancer has been suggested by other studies, but not all of the findings are consistent with ours. Most epidemiologic studies conducted to date have been modest in size, with nonsignificant findings, and have included both smokers and nonsmokers. There are similar distributions of studies reporting increased and decreased risks associated with an earlier age at menarche, a later age at menopause, a longer reproductive period, and an increased parity (11–22). With respect to prospective studies, a cohort analysis of Japanese female nonsmokers observed an increased risk of lung cancer with early age at menarche and late age at menopause (17). Contrary to our findings, those of a recent study of female Canadian smokers and nonsmokers showed increased risks of lung cancer among women with a higher parity and an earlier age at first livebirth (14). Case-control studies have also reported conflicting results. Similar to our findings, those of 2 studies from East Asia demonstrated reduced risks of lung adenocarcinoma among women with longer menstrual cycle length (13, 18) and higher parity (18); however, there were no associations of age at menarche or age at menopause. These studies are similar to ours, with one of them conducted in Shanghai (13) and the other observing the strongest decreased risks among lifetime nonsmokers and adenocarcinoma cases (18). Another Chinese study (11) observed findings similar to ours for later age at menopause; however, later age at menarche was also associated with a decreased risk, and there were no associations for length of menstrual cycle or parity. Contrary to our results, those of studies conducted in both the United States (19) and China (21) demonstrated increased risks of adenocarcinoma among women with a later age at menopause. However, no associations were observed between the age at menarche or parity and lung cancer. The retrospective designs, inclusion of smokers, and modest sample sizes (with the exception of 1 study (21)) could have contributed to the disparate findings reported in these studies compared with ours.

The relatively small effect of direct smoking observed in this cohort is similar to that reported by prior studies in other Chinese populations (13, 14, 20, 21). Estimates tend to be much higher among current smokers than among former smokers or ever smokers (current and former combined) and, in this study, women were classified as ever/never smokers.

Our findings of a lower risk of lung cancer among women with a normal or later age at menopause compared with those women who underwent earlier menopause (<46 years of age) suggest that there is something about an early age at menopause that increases risk. One possible explanation is that a greater proportion of women who underwent earlier age at menopause did so through surgical means and thus were different from women who experienced a later age at natural menopause. Similar results, however, were observed when analyses were restricted to women who experienced natural menopause. The findings for age at menarche also

hold up when restricted to women with a later age at menopause, suggesting that features of both menarche and menopause might be important.

The mechanism through which menstrual factors could influence lung cancer risk is not entirely clear. It has been hypothesized that ages at menarche and menopause are markers of nutritional status (33, 34). However, risk estimates were not attenuated after adjustment for various nutritional factors. A potential mechanism through which menstrual factors could influence risk is by the role of estrogens in epithelial cell regeneration and maintenance. Localized estrogen receptors are important for cellular maintenance in the lung (35, 36). Surfactant, produced in alveolar type II cells, is essential for normal lung function; it clears the lungs of unwanted particles, including carcinogens. Lungs from adult female estrogen receptor-beta knockout mice have larger, yet fewer alveoli than their wild-type littermates and accumulate surfactant inside the alveolar spaces (36). In addition, sex differences in immune function suggest that hormonal influences play a role. Women have higher systemic immunity and are more susceptible to autoimmune diseases than are men (37, 38). In murine models, treatment of normal mice with estrogen leads to the induction of antibodies (39–42). In vivo and in vitro models demonstrate the role of estrogens in influencing the cytokine milieu toward pro- (type I) or antiinflammatory (type II) cytokines (37). Interstitial lung disease, characterized by chronic inflammation and fibrosis, is hypothesized to predispose to lung carcinogenesis via repeated cellular injury and genetic damage to local epithelial cells. Therefore, a mechanistic link among estrogen exposure, inflammation in the lung, and lung cancer is biologically plausible.

The main strength of our study is the inclusion of a large number of nonsmoking women with information on passive smoke exposure. Participants have been followed prospectively with a high rate of follow-up. There are, however, some limitations. Although our sample size as a whole is large, the number of cases accrued to date is modest. In addition, we were not sufficiently powered to examine the associations of exogenous hormone use on risk, since few women in our study population were exposed. Self-reported ages at menopause and menarche are subject to misclassification, but we expected that to be random and, thus, they serve only to attenuate the observed risk estimates. Finally, although we included ever exposure to passive smoke (at home or in the workplace) in the model, we acknowledge that this may not have fully controlled for confounding given that there was no overall association. Although a stronger association was observed when women were classified on exposure at work alone, adjustment for workplace exposure did not materially alter risk estimates. In addition, although less dramatic effects were observed among women who reported no passive smoke exposure, the number of cases and total person-years are much lower than those for women who reported exposure to passive smoke.

The risk of lung cancer among female lifetime nonsmokers was decreased for women with a later age at menopause, a longer reproductive period, and an increased parity. Later age at menarche was associated with increased risk. These findings suggest a potential role for hormonal factors in the etiology of lung cancer in nonsmoking women. The accumulating laboratory evidence is likely sufficient to justify targeted molecular epidemiologic analyses that test these hypotheses among nonsmoking women whose reproductive history and exposure to exogenous estrogen are well-characterized.

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