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Tobacco Smoking Modifies the Association between Hormonal Factors and Lung Cancer Occurrence among Post-Menopausal Chinese Women[1]

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Abstract

Inconsistent evidence has been reported on the role of female hormonal factors in the development of lung cancer. This population-based case–control study evaluated the main effect of menstrual/reproductive factors on the risk of lung cancer, and the effect modification by smoking status. Multivariable unconditional logistic regression models were applied adjusted for age, income, education, county of residence, body mass index, smoking status, pack-years of smoking, and family history of lung cancer. Among 680 lung cancer cases and 1,808 controls, later menopause (at >54 vs. <46 years old) was associated with increased risk of lung cancer (SBOR, semi-Bayes adjusted odds ratio = 1.61, 95% PI, posterior interval = 1.10–2.36). More pregnancies (2 or 3 vs. 0 or 1) was associated with decreased risk (SBOR = 0.71, 95% PI = 0.53, 0.95). Ever being a smoker and having two or fewer pregnancies in one's lifetime could jointly increase the odds of lung cancer (RERI, relative excess risk due to interaction = 1.71, 95% CI = 0.03, 3.38). An increased number of ovulatory cycles was associated with increased risk of lung cancer (SBOR for 13 ovulatory cycles = 1.02, 95% CI = 1.00+, 1.04).

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Introduction

Lung cancer is the most common and deadly cancer with the highest number of new cases (2,093,876) and deaths (1,761,007) in 2018 according to GLOBOCAN estimation [1]. It was also estimated that 37.0% of new lung cancer cases and 39.2% of lung cancer deaths happened in China in 2018 [2]. According to the CONCORD-3 study [3]and SEER project [4], the 5-year survival rate of lung cancer was 19.8% in China and 21.2% in the USA.

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Tobacco smoking is believed to be the leading cause of lung cancer [5], with very high attributable risks (about 90% for men and 60% for women [6]) and odds ratios (23.6 for current male smokers and 7.8 for current female smokers respectively [6,7]. Smoking is more strongly associated with squamous cell carcinoma (SCC) and small cell carcinoma than with adenocarcinoma.

In smokers, pack-years [7–9] of smoking, cumulative tar exposure in tobacco products [10] and smoking intensity [7] are positively associated with the risk of lung cancer. Among non-smokers, environmental tobacco smoking (ETS or second hand smoking) has been shown associated with increased risk of lung cancer for all major histologic types [9].

Men and women differ in terms of lung cancer risk, survival, histology, and genetics. In the US, the lung cancer incidence rate in men peaked around the 1980s and decreased since the 1980s. On the other hand, rates continued to rise among women until 2010 [11] and started to drop in the past couple of years [12]. Women tend to have increased risk of getting lung cancer among non-smokers [13–15] and women have better lung cancer survival than men globally. According to GLOBOCAN estimation in 2018 [1], 34.6% of new lung cancer cases and 32.7% lung cancer deaths happened in women. There is a lower proportion of SCC and a higher proportion of adenocarcinoma in women than in men [14]. In NSCLC (non-small cell lung cancer) patients, EGFR (Epidermal growth factor receptor) mutations are more frequent in female than in male (more than 40% vs. less than 15%) [16]. Among current smokers, female patients had a 3.9-fold median level of CYP1A1 (Cytochrome P450 1A1) mutation compared to males [17]. After all measurable lifestyle and unchangeable factors are accounted for, the occurrences of lung cancer are still imbalanced between men and women [13–15]. These facts suggested that female sex hormones, especially estrogen, may have played a role in the initiation and progression of lung tumors [13,14].

Estrogen has long been associated with cancer development [18,19]. The amount of circulating estrogen and exogenous estrogen determines the effect of ERs (estrogen receptor) on cell proliferation and carcinogenesis. Menstrual and reproductive factors are commonly used as proxies for life-long endogenous estrogen exposure in women, while oral contraceptive use (OC) and hormone replacement therapy (HRT) represent exogenous sources of estrogen.

The results from epidemiologic studies on hormonal factors and the risk of lung cancer [20–27] were generally inconsistent [28]. In order to improve the validity and precision in the investigation of the associations between menstrual/reproductive history and the risk of lung cancer, and to investigate the effect modification by smoking status, we conducted the present analysis using data from the Jiangsu Four Cancers (JFC) Study.

Materials and Methods

Population

The JFC Study is a large-scale, population-based case–control study of cancers of the lung, liver, stomach, and esophagus conducted in four counties in Jiangsu, China. It was carried out in an effort to obtain high-quality data to investigate the lifestyle, environmental, and genetic factors associated with the four major cancers in China [29].

The incident primary lung cancer cases were reported by CDC-managed local cancer registries between January 1, 2003 and December 31, 2010. Diagnoses were either pathologically or clinically confirmed within 1 year of interview. Cases were required to be female, at least 18 years old, residents of the respective county for at least 5 years, and in a stable medical condition as determined by their physicians. Premenopausal cases were excluded because their estrogen biosynthesis and metabolism are different from postmenopausal women [30,31]. Post-menopausal cases who had undergone induced menopause (menopause due to surgery, radiotherapy, and other reasons) were also excluded [29]. There were a total of 680 cases eligible for the present analysis.

Controls of the JFC Study were females randomly selected from the same county as the cases. The JFC Study individually matched controls to cases by age (+/− 5 years). In the present analysis, all postmenopausal female controls from controls for four cancer sites were combined in order to increase statistical power. The same as cases, controls are those with natural menopause only. A total of 1808 controls were eligible for the present analysis.

A standardized epidemiological questionnaire including demographic characteristics, social economic status and menstrual/reproductive history, and other risk or protective factors were employed to collect data for both cases and controls by face-to-face interview. The interviewers were trained and the questionnaire was field tested as detailed in a previous study [32]. The quality of participants' answers was validated logically by repeated or related questions. A variable was coded as missing if the participant had inconsistent answers to the repeated/related questions.

Exposure Ascertainment

The standard epidemiological questionnaire collected information on exposures of interest, which were hormonal factors including age at menarche and menopause, parity, gravidity, live birth, outcome of first pregnancy, induced abortion, and oral contraceptive (OC) use. The outliers of ages at menarche and menopause, as well as contradictory answers in reference to current age, were treated as missing data. The normal distributions of ages at menarche and menopause were compared to large observational studies conducted in China among women with similar years of births in the JFC Study [33,34]. Three-sigma rule of thumb [35] was used to identify outliers for these two variables. Reproductive window was calculated as the difference between age at menopause and menarche. Gravidity and parity are the numbers of times a female has been pregnant and carried the pregnancies to a viable gestational age, respectively. Therefore, gravidity was calculated as the sum of numbers of miscarriages, abortions, live births, stillbirths and all other outcomes of pregnancy. Parity was calculated as the total number of live births and stillbirths [36]. Missing data in number of live births, miscarriages, induced abortions and stillbirths were imputed with the medians in the control group. The number of ovulatory cycles was calculated based on the reproductive window, subtracted by the length of time without ovulation due to OC use, live births, stillbirths, miscarriages, induced abortions, and breast feeding [37,38]. It was calculated assuming 36, 28, 12, and 12 weeks of no ovulatory cycles due to a live birth, a stillbirth, a miscarriage, and an induced abortion, respectively. It was also assumed that there was no ovulation during OC use. If the participant's answer to the breastfeeding question was ‘breast feeding only’, ‘no breast feeding’, and ‘mixed feeding’, the length of time without ovulatory cycles after delivery was assumed to be 24, 6, and 9 months, respectively. Twenty-eight days was applied as the average length of an ovulatory cycle and 52.178 weeks in a year was assumed. In the study of

interaction with smoking status, selected menstrual and reproductive factors were dichotomized in order to calculate RERI (relative excess risk due to interaction) and ROR (ratio of the odds ratios).

The questionnaire also collected information on demography and covariates: age at interview, county of residence, income, education, smoking status, pack-years of smoking, body mass index (BMI), and family history of lung cancer. Age at interview was calculated based on self-reported date of birth. If the participant only remembered the lunar month of birth, the following solar month was used as the proxy. There were no missing data for year of birth. In cases of missing month or date of birth, the median values (July and 15th, respectively) were used as the estimations. BMI cut points were chosen for underweight (<18.5 kg/m^2), normal weight (18.5 kg/m^2 to <24 kg/m^2), overweight (24 kg/m^2 to <28 kg/m^2) and obesity (> = 28 kg/m^2) according to the standards for Chinese populations [39]. Ever smoking was defined as having smoked more than 100 cigarettes in one's lifetime. The missing values for pack-years of smoking (missing rate = 12.6%) were imputed with the county, sex, and age-specific median values of the controls. Family history of lung cancer was defined as lung cancer diagnosis in any family member including parents, grandparents, siblings, children, spouses, and parents' siblings. Income was measured as the per-capita annual income of the household including wages, bonuses, and allowances on an average over the most recent decade.

Statistical Analysis

Cases and controls were compared using the χ^2 test for categorical variables and the Student t-test for continuous variables. The Mantel trend test was used to assess whether an association was exhibiting a linear trend. The main effect was tested with multivariable unconditional logistic regression models, adjusting for covariates. According to a priori biological rationale [5,27,40,41], age, county, BMI, exposure to tobacco smoking, pack-years of smoking, family history of lung cancer, income, and education were adjusted for. Stratified analysis by smoking status was performed. In addition, age at menarche was adjusted for in the analysis for age at menopause and age at first birth; length of reproductive window was adjusted for in the analysis for parity/gravidity/number of children; age at first birth was adjusted for in the analysis for outcome of first birth. Odds ratios and 95% confidence intervals were calculated for all the possible associations. Semi-Bayes estimates and 95% posterior intervals were calculated to mitigate the influence from sparse data and multiple comparisons [42]. In the semi-Bayes estimation, the priors of coefficients in the logistic regressions were assigned normal distributions with mean of zero and variance of 0.5 (corresponding to OR = 1, 95% PI = 0.25–4). And the priors were updated with observed values from the study population. Therefore, the SB adjusted ORs have shrunk towards the null. The effect modification by tobacco smoking was calculated by RERI for the additive scale and was by ROR for the multiplicative scale. In these calculations, age, county, BMI, family history of lung cancer, income, and education were adjusted for.

Complete case analyses were applied except where imputation was described in "Exposure ascertainment". The missing rates of those variables with complete case analyses were all less than 10%. SAS version 9.4 was used for statistical analysis. All p-values were based on $\alpha = 0.05$ (two-sided). The JFC study was approved by the Human Subject Protection Committees of the Jiangsu Provincial Center for Disease Control (CDC) and the University of California at Los Angeles (UCLA). Informed consent was obtained from all participants upon study enrollment.

Results

Summary Statistics

The average age in this post-menopausal female population was 67.21 years. Table 1 summarized the distribution of demographic and major risk factors. Cases and controls showed similar average ages and education/income distributions. Ganyu and Tongshan Counties contributed more lung cancer cases while Dafeng and Chuzhou counties contributed more controls. Significantly higher proportions of smokers and larger pack-years were observed in lung cancer cases than in controls. Cases were significantly more likely to be underweight and less likely to be overweight or obese than controls. Family history of lung cancer tended to happen among lung cancer cases rather than controls.

Menstrual Characteristics

According to Table 2-1, there was no significant statistics for the relationship between age at menarche and risk of lung cancer in the entire study population. However, we found an 35% increased odds (Table 2-2) among never smoking subpopulation, comparing age at menarche between 16 and 17 years old with that <=15 years old (SBOR: semi-Bayes adjusted odds ratio = 1.35, 95% PI, posterior interval = 1.01–1.80). The Mantel test P-value was 0.03, indicating a

Table 1. The Distribution of Demographic and Major Risk Factors in Cases and Controls

	Lung Cancer	Controls	*P*
Total Number	680 (27.33)	1808 (72.67)	
	Mean(SD)	**Mean(SD)**	
Age (continuous)	66.79 (9.36)	67.37 (9.32)	.1641
	N(column%)	**N(column%)**	
Education			.1783
Illiterate	554 (81.71)	1431 (79.50)	
Primary School	106 (15.63)	294 (16.33)	
Middle School +	18 (2.65)	75 (4.17)	
Income			.1783
<1000	130 (19.88)	416 (23.44)	
1000–1499	131 (20.03)	382 (21.52)	
1500–2499	177 (27.06)	459 (25.86)	
> = 2500	216 (33.03)	518 (29.18)	
County			**<.0001**
Dafeng	152 (22.35)	597 (33.02)	
Ganyu	185 (27.21)	337 (18.64)	
Chuzhou	120 (17.65)	365 (20.19)	
Tongshan	223 (32.79)	509 (28.15)	
Tobacco smoking			**<.0001**
Ever	181 (26.62)	344 (19.03)	
Never	499 (73.38)	1464 (80.97)	
Pack-year			**<.0001**
0	499 (73.38)	1464 (80.97)	
<10	25 (3.68)	68 (3.76)	
[10,20)	24 (3.53)	63 (3.48)	
[20,30)	51 (7.50)	91 (5.03)	
[30,40)	19 (2.79)	45 (2.49)	
[40,50)	25 (3.68)	33 (1.83)	
[50,60)	12 (1.76)	24 (1.33)	
> = 60	25 (3.68)	20 (1.11)	
BMI			**<.0001**
<18.5	115 (17.09)	155 (8.61)	
18.5 to <24	388 (57.65)	998 (55.41)	
24 to <28	137 (20.36)	497 (27.60)	
> = 28	33 (4.90)	151 (8.38)	
Family history of lung cancer			**.0117**
Yes	25 (3.68)	35 (1.94)	
No	655 (96.32)	1773 (98.06)	

Table 2-1. Menstrual and Reproductive Factors in Association with the Risk of Lung Cancer in the Entire Study Population

	All					
	Cases, n = 680		Ctrls, n = 1808		Adjusted OR[1]	SB-adjusted[1] OR[1]
	N	%	N	%	(95% CI)	(95% PI)
Menstrual Characteristics						
Age at menarche						
<=15	224	33.33	639	35.56	1.00 (Ref)	1.00 (Ref)
16–17	262	38.99	689	38.34	1.20 (0.96, 1.51)	1.20 (0.96, 1.50)
> = 18	186	27.68	469	26.10	1.29 (1.00-, 1.68)	1.29 (1.00-, 1.66)
P^4_{trend}					**0.046**	**0.043**
As a continuous variable[8]					1.05 (1.00-, 1.10)	1.05 (1.00-, 1.10)
Age at menopause[5]						
<46	62	9.84	189	11.09	1.00 (Ref)	1.00 (Ref)
46–54	451	71.59	1307	76.66	1.02 (0.73, 1.43)	1.01 (0.73, 1.38)
>54	117	18.57	209	12.26	**1.65 (1.10, 2.48)**	**1.61 (1.10, 2.36)**
P_{trend}					**0.004**	**0.004**
As a continuous variable[8]					**1.03 (1.01, 1.06)**	**1.03 (1.01, 1.06)**
Reproductive window						
<=32	227	35.80	651	38.11	1.00 (Ref)	1.00 (Ref)
33–35	181	28.55	511	29.92	0.98 (0.76, 1.25)	0.98 (0.77, 1.24)
> = 36	226	35.65	546	31.97	1.10 (0.87, 1.40)	1.10 (0.87, 1.40)
P_{trend}					0.441	0.406
As a continuous variable[8]					1.01 (0.99, 1.03)	1.01 (0.99, 1.03)
Reproductive History						
Parity[6]						
0 or 1	116	17.08	217	12.00	1.00 (Ref)	1.00 (Ref)
2–3	305	44.92	864	47.79	**0.68 (0.51, 0.91)**	**0.70 (0.53, 0.93)**
4 or more	258	38	727	40.21	**0.72 (0.53, 0.97)**	**0.74 (0.55, 0.99)**
P_{trend}					0.177	0.18
As a continuous variable[8]					0.95 (0.89, 1.01)	0.95 (0.89, 1.01)
Gravidity[6]						
0 or 1	104	15.32	195	10.79	1.00 (Ref)	1.00 (Ref)
2–3	275	40.50	773	42.75	**0.69 (0.50, 0.93)**	**0.71 (0.53, 0.95)**
4 or more	300	44.18	840	46.46	0.78 (0.58, 1.06)	0.80 (0.60, 1.08)
P_{trend}					0.583	0.587
As continuous variable[8]						
Number of live birth[6]						
0 or 1	118	17.38	226	12.50	1.00 (Ref)	1.00 (Ref)
2–3	313	46.10	887	49.06	**0.69 (0.52, 0.92)**	**0.71 (0.54, 0.94)**
4 or more	248	36.52	695	38.44	**0.73 (0.54, 0.99)**	0.75 (0.56, 1.01)
P_{trend}					0.227	0.227
As a continuous variable[8]					0.95 (0.89, 1.01)	0.95 (0.89, 1.01)
Life time abortion						
Never	631	92.93	1650	91.26	1.00 (Ref)	1.00 (Ref)
Ever	48	7.07	158	8.74	1.03 (0.70, 1.51)	1.01 (0.70, 1.45)
As a continuous variable[8]					1.08 (0.84, 1.39)	1.05 (0.83, 1.34)
Outcome of first pregnancy[7]						
Live birth	631	94.89	1656	94.04	1.00 (Ref)	1.00 (Ref)
Stillbirth	19	2.86	51	2.90	0.88 (0.48, 1.61)	0.91 (0.52, 1.58)
Miscarriage	14	2.11	46	2.61	1.02 (0.53, 1.97)	1.03 (0.57, 1.87)
Ectopic Preg	1	0.15	1	0.06	NA	0.91 (0.24, 3.49)
Induced abortion	0	0	6	0.34	NA	NA
Number of Ovulatory Cycles						
<=368	182	30.18	536	33.58	1.00 (Ref)	1.00 (Ref)
(368, 415]	192	31.84	537	33.65	0.96 (0.74, 1.24)	0.96 (0.75, 1.23)
>415	229	37.98	523	32.77	1.21 (0.94, 1.55)	1.21 (0.95, 1.55)
P_{trend}					0.123	0.113
As a continuous variable (per 13 ovulatory cycles) [8]					**1.02 (1.00+, 1.04)**	**1.02 (1.00+, 1.04)**
Exogenous Hormone						
Oral Contraceptive use						
Never	635	96.5	1649	94.66	1.00 (Ref)	1.00 (Ref)
Ever	23	3.50	93	5.34	0.93 (0.56, 1.55)	0.93 ((0.58, 1.50)

possible dose–response relationship. Compared with ages at menopause between 46 and 54 years, those later than 54 years old were associated with 1.61 times of odds of lung cancer occurrence in the whole study population (Table 2-1, SBOR = 1.61, 95% PI = 1.10–2.36, Mantel test P-value = 0.023). Age at menopause also showed 3% increased odds of lung cancer per one-year increase (SBOR = 1.03, 95% PI = 1.01–1.06). This aforementioned association for age at menopause seemed to exist among never smokers but could not be found in the ever-smoking subpopulation (Table 2-2). There was no evidence demonstrating an association between the length of reproductive window and the risk of lung cancer.

Reproductive History

As reported in Table 2-1, a parity between two and three showed 30% and a parity of four or more showed 26% decreased odds in lung cancer occurrence, (parity = 2 or 3: SBOR = 0.70, 95% PI =

Table 2-2. Menstrual and Reproductive Factors in Association with the Risk of Lung Cancer, by Smoking Status

	Never Smokers						Ever Smokers					
	Cases, n = 499		Ctrls, n = 1464		Adjusted OR[2]	SB-adjusted OR[2]	Cases, n = 181		Ctrls, n = 344		Adjusted OR[3]	SB-adjusted OR[3]
	N	%	N	%	(95% CI)	(95% PI)	N	%	N	%	(95% CI)	(95% PI)
Menstrual Characteristics												
Age at menarche												
<=15	175	35.57	553	37.93	1.00(Ref)	1.00(Ref)	49	27.22	86	25.37	1.00(Ref)	1.00(Ref)
16–17	187	38.01	534	36.63	1.25 (0.96, 1.64)	1.26 (0.98, 1.63)	75	41.67	155	45.72	0.94 (0.57, 1.53)	0.94 (0.60, 1.48)
> = 18	130	26.42	371	25.45	1.34 (0.99, 1.82)	**1.35 (1.01, 1.80)**	56	31.11	98	28.91	1.01 (0.59, 1.74)	1.02 (0.62, 1.67)
P^4_{trend}					**0.050**	**0.03**					0.962	0.953
As a continuous variable[8]					1.04 (0.98, 1.11)	1.05 (0.99, 1.11)					1.05 (0.94, 1.17)	1.05 (0.94, 1.17)
Age at menopause[5]												
<46	48	10.39	147	10.71	1.00 (Ref)	1.00 (Ref)	14	8.33	42	12.65	1.00 (Ref)	1.00 (Ref)
46–54	319	69.05	1041	75.82	0.90 (0.61, 1.33)	0.91 (0.64, 1.30)	132	78.57	266	80.12	1.48 (0.72, 3.06)	1.23 (0.68, 2.21)
>54	95	20.56	185	13.47	1.45 (0.91, 2.29)	1.45 (0.95, 2.20)	22	13.1	24	7.23	2.48 (0.94, 6.51)	1.80 (0.85, 3.84)
P_{trend}					**0.035**	**0.023**					0.066	0.077
As a continuous variable[8]					1.03 (1.00-, 1.06)	**1.03 (1.00+, 1.06)**					1.04 (0.98, 1.10)	1.04 (0.98, 1.10)
Reproductive window												
<=32	151	32.54	503	36.53	1.00 (Ref)	1.00 (Ref)	76	44.71	148	44.71	1.00 (Ref)	1.00 (Ref)
33–35	134	28.88	409	29.70	1.00 (0.75, 1.35)	1.03 (0.78, 1.37)	47	27.65	102	30.82	0.79 (0.48, 1.30)	0.82 (0.51, 1.31)
> = 36	179	38.58	465	33.77	1.13 (0.86, 1.50)	1.16 (0.89, 1.51)	47	27.65	81	24.47	0.95 (0.57, 1.59)	0.97 (0.60, 1.57)
P_{trend}					0.375	0.274					0.749	0.778
As a continuous variable[8]					1.01 (0.98, 1.04)	1.01 (0.99, 1.04)					1.01 (0.96, 1.06)	1.01 (0.96, 1.06)
Reproductive History												
Parity[6]												
0 or 1	80	16.06	176	12.02	1.00 (Ref)	1.00 (Ref)	36	19.89	41	11.92	1.00 (Ref)	1.00 (Ref)
2–3	242	48.59	753	51.43	**0.69 (0.49, 0.97)**	0.73 (0.53, 1.00+)	63	34.81	111	32.27	0.67 (0.35, 1.27)	0.76 (0.43, 1.35)
4 or more	176	35.34	535	36.54	0.74 (0.52, 1.08)	0.84 (0.60, 1.18)	82	45.30	192	55.81	**0.52 (0.28, 0.97)**	0.60 (0.35, 1.03)
P_{trend}					0.332	0.62					0.114	0.116
As a continuous variable[8]					0.95 (0.88, 1.03)	0.97 (0.90, 1.04)					0.91 (0.81, 1.01)	0.91 (0.81, 1.01)
Gravidity[6]												
0 or 1	71	14.26	159	10.86	1.00 (Ref)	1.00 (Ref)	33	18.23	36	10.47	1.00 (Ref)	1.00 (Ref)
2–3	222	44.58	677	46.24	0.73 (0.51, 1.05)	0.77 (0.55, 1.07)	53	29.28	96	27.91	0.57 (0.29, 1.12)	0.67 (0.37, 1.21)
4 or more	205	41.16	628	42.90	0.82 (0.57, 1.20)	0.92 (0.65, 1.30)	95	52.49	212	61.63	0.54 (0.29, 1.00+)	0.62 (0.36, 1.08)
P_{trend}					0.684	0.902					0.268	0.263
As continuous variable[8]					0.98 (0.91, 1.05)	1.00 (0.93, 1.07)					**0.89 (0.81, 0.99)**	**0.89 (0.81, 0.99)**
Number of live birth[6]												
0 or 1	82	16.47	183	12.50	1.00 (Ref)	1.00 (Ref)	36	19.89	43	12.5	1.00 (Ref)	1.00 (Ref)
2–3	249	50	770	52.60	**0.69 (0.49, 0.98)**	0.74 (0.54, 1.01)	64	35.36	117	34.01	0.67 (0.36, 1.27)	0.76 (0.43, 1.33)
4 or more	167	33.53	511	34.90	0.75 (0.52, 1.09)	0.84 (0.60, 1.18)	81	44.75	184	53.49	0.56 (0.31, 1.04)	0.64 (0.37, 1.09)
P_{trend}					0.339	0.58					0.206	0.205
As a continuous variable[8]					0.94 (0.87, 1.02)	0.94 (0.87, 1.02)					0.92 (0.82, 1.03)	0.92 (0.82, 1.03)
Life time abortion												
Never	463	92.97	1351	92.28	1.00 (Ref)	1.00 (Ref)	168	92.82	299	86.92	1.00 (Ref)	1.00 (Ref)
Ever	35	7.03	113	7.72	1.29 (0.81, 2.06)	1.23 (0.81, 1.87)	13	7.18	45	13.08	0.62 (0.31, 1.25)	0.66 (0.36, 1.22)
As a continuous variable[8]					0.66 (0.38, 1.16)	1.20 (0.92, 1.56)					0.66 (0.38, 1.16)	0.68 (0.41, 1.13)
Outcome of first pregnancy[7]												
Live birth	460	94.65	1361	94.91	1.00 (Ref)	1.00 (Ref)	171	95.53	295	90.21	1.00 (Ref)	1.00 (Ref)
Stillbirth	15	3.09	36	2.51	1.05 (0.51, 2.15)	1.15 (0.62, 2.12)	4	2.23	15	4.59	0.43 (0.11, 1.61)	0.64 (0.26, 1.60)
Miscarriage	11	2.26	1	0.07	1.68 (0.76, 3.69)	1.59 (0.81, 3.11)	3	1.68	17	5.20	0.27 (0.07, 1.01)	0.49 (0.20, 1.19)
Ectopic Preg	0	0	29	2.02	NA	NA	1	0.56	0	0	NA	NA
Induced abortion	0	0	6	0.42	NA	NA	0	0	0	0	NA	NA
Number of Ovulatory Cycles												
<=366	124	27.93	413	31.97	1.00 (Ref)	1.00 (Ref)	58	36.48	123	40.46	1.00 (Ref)	1.00 (Ref)
367–413	139	31.31	432	33.44	0.99 (0.73, 1.34)	0.97 (0.73, 1.30)	53	33.33	105	34.54	0.91 (0.55, 1.52)	0.92 (0.57, 1.47)
> = 414	181	40.77	447	34.60	1.18 (0.88, 1.59)	1.22 (0.92, 1.61)	48	30.19	76	25	1.16 (0.68, 2.00)	1.15 (0.70, 1.89)
P_{trend}					0.233	0.135					0.63	0.632
As a continuous variable (per 13 ovulatory cycles) [8]					1.02 (0.99, 1.04)	1.02 (1.00-, 1.04)					1.02 (0.98, 1.06)	1.02 (0.98, 1.07)
Exogenous Hormone												
Oral Contraceptive use												
Never	465	96.47	1327	95.06	1.00 (Ref)	1.00 (Ref)	170	96.59	312	93.13	1.00 (Ref)	1.00 (Ref)
Ever	17	3.53	69	4.94	1.16 (0.63, 2.14)	1.11 (0.64, 1.93)	6	3.41	23	6.87	0.58 (0.22, 1.54)	0.69 (0.32, 1.49)

Notation:

1. Odds ratios and 95% confidence intervals adjusted for age (as a continuous variable), smoking status (ever or never), pack-years of smoking, family history of lung cancer (yes or no), income, education, county of residence, and BMI.
2. Odds ratios and 95% confidence intervals adjusted for age (as a continuous variable), family history of lung cancer (yes or no), income, education, county of residence, and BMI.
3. Odds ratios and 95% confidence intervals adjusted for age (as a continuous variable), pack-years of smoking, family history of lung cancer (yes or no), income, education, county of residence, and BMI.
4. Mantel trend test.
5. Additional adjustment for age at menarche (as a continuous variable).
6. Additional adjustment for length of reproductive window.
7. Additional adjustment for age at first birth.
8. Absolute number/count as the continuous variable.

Table 3. Interaction with Smoking Status

Factor		Case/Ctrl	aOR (95%CI)[1]	Interactions (95%CI)[1]
Menarche at 17 or later	Ever smoking			
No	No	275/838	1.00(Ref)	
No	Yes	94/170	**2.36 (1.70, 3.27)**	RERI = −0.43 (−1.36, 0.5)
Yes	No	217/620	**1.28 (1.02, 1.61)**	ROR = 0.73 (0.47, 1.14)
Yes	Yes	86/169	**2.21 (1.56, 3.12)**	
Menopause at 55 or later	Ever smoking			
No	No	367/1188		
No	Yes	146/308	**1.98 (1.51, 2.59)**	RERI = 0.87 (−1.39, 3.12)
Yes	No	95/185	**1.60 (1.19, 2.15)**	ROR = 1.09 (0.53, 2.25)
Yes	Yes	22/24	**3.45 (1.80, 6.60)**	
Parity	Ever smoking			
Parity> = 3	No	335/1069		
Parity> = 3	Yes	129/276	**1.86 (1.40, 2.48)**	RERI = 0.96 (−0.39, 2.3)
Parity = 0, 1 or 2	No	163/395	**1.32 (1.03, 1.69)**	ROR = 1.28 (0.76, 2.15)
Parity = 0, 1 or 2	Yes	52/68	**3.13 (2.03, 4.83)**	
Gravidity	Ever smoking			
Gravidity> = 3	No	352/1111		
Gravidity> = 3	Yes	132/290	**1.77 (1.33, 2.34)**	**RERI = 1.71 (0.03, 3.38)**
Gravidity = 0, 1 or 2	No	146/353	1.26 (0.98, 1.62)	ROR = 1.68 (0.98, 2.89)
Gravidity = 0, 1 or 2	Yes	49/54	**3.73 (2.36, 5.90)**	
#live birth = 0, 1 or 2	Ever smoking			
No	No	333/1058		
No	Yes	128/273	**1.85 (1.39, 2.47)**	RERI = 0.95 (−0.36, 2.27)
Yes	No	165/406	**1.30 (1.01, 1.66)**	ROR = 1.29 (0.77, 2.16)
Yes	Yes	53/71	**3.10 (2.02, 4.76)**	

Notation:
Point estimates and 95% confidence intervals were adjusted for age (as a continuous variable), family history of lung cancer (yes or no), income, education, county of residence, and BMI (categorical).

0.53–0.93, parity = 4 or more: SBOR = 0.74, 95% PI =0.55–0.99, reference group is parity = 1). The dose–response trend and change per unit increase in parity were not statistically significant (P_{trend} = .177 and the semi-Bayes posterior interval was across the null). Among never smoking or ever smoking subpopulation (Table 2-2), there seemed to be no association between parity and the risk of lung cancer. A moderate gravidity seemed to decrease risk of lung cancer by 29% (SBOR = 0.71, 95% PI = 0.53–0.95, gravidity = 2–3 compared with gravidity = 0 or 1) in the study population (Table 2-1). Among never smokers, gravidity did not show a significant relationship with the risk of lung cancer. On the other hand, treated as a continuous variable, a one-unit increase in gravidity was significantly associated with 11% decrease in risk of lung cancer (SBOR = 0.89, 95% PI = 0.81–0.99) for ever-smokers. A moderate number of live births was shown associated with 29% decreased risk of lung cancer in all the post-menopausal women (SBOR = 0.71, 95% PI = 0.43–0.94, number of live birth = 2–3 compared with 0–1). However, this statistical significance for number of live births was not observed in either ever- or never- smokers (Table 2-2).

Induced abortion, reported or not in Tables 2-1 and 2-2, did not show any significant associations with lung cancer. A statistically significant association between an increase of 13 ovulatory cycles (about 1 year) and 2% increase in the risk of lung cancer was shown in our post-menopausal study population (SBOR = 1.02, 95% PI = (1.00+, 1.04)) but not observed in subpopulations stratified by smoking status.

Exogenous Hormone Use

Tables 2-1 and 2-2 didn't show a relationship between OC use and risk of lung cancer.

Effect Modification by and Interaction with Smoking Status

Tests for interaction with smoking status on additive and multiplicative scales were performed for menstrual and reproductive factors that showed statistically significant main effects. As reported in Table 3, gravidity at or below two showed an RERI of 1.71 with 95% CI of 0.33–3.38. The ROR of gravidity was 1.68 without statistical significance. These RERIs and RORs were suggesting superadditivity for the interaction between smoking and gravidity (Table 3).

Discussion

In the present analysis of hormonal factors, after controlling for potential confounders and correction by semi-Bayes shrinkage, later menopause was found to be associated with increased risk of lung cancer. This relationship remained in the never-smoking subpopulation, but disappeared in the ever-smoking subpopulation. A higher parity, gravidity, and number of live births were respectively associated with reduced risk of lung cancer. Increased number of ovulatory cycles was associated with increased risk of lung cancer. Other hormonal factors such as reproductive window, number of abortions, and outcomes of first pregnancy were not associated with lung cancer risk in our study population.

The stratified analyses for never- and ever-smokers indicated that reproductive factors might interact with smoking status in the development of lung cancer. Superadditivity was corroborated by RERIs, showing a considerably greater joint effect of smoking and low gravidity than expected under an additive model without interactions.

Between 1/1/1988 and 7/31/2018, there were a total of 27 epidemiologic studies [20–27] that tested for associations between hormonal factors and risk of lung cancer. A meta-analysis [26] showed a statistically significant decreased risk of lung cancer with older age at menarche among Caucasian-dominated North American female populations. The effect of hormonal factors on lung cancer varies by race/ethnicity and is inconsistent among Asian populations. In our JFC Study, a menarche age greater than 18 years old could be a marker of poor childhood nutritional status, which has long-term adverse influence on health [23,43,44]. This increased risk by later

menarche was also found in six other studies conducted among Chinese women [23,25,27,45–47] although there was one study with potentially decreased risk linked to late menarche [22].

A greater menopausal age was proposed to increase the risk of lung cancer since a greater menopausal age means more exposure to estrogen [18,19]. However, an ILCCO pooled analysis [20] with a considerable number of missing values for exposure variables didn't show a significant result for this relationship. An Asian (Singapore, SBCSP) cohort study [23] showed null associations without adjusting for smoking intensity or pack-years of smoking, leaving potential residual confounding by smoking. In this present JFC Study, where missing information was minimal and pack-years of smoking was adjusted, significantly increased risk by greater age at menopause was found. This finding was corroborated by two other studies among Chinese women [25,27].

In this present study, higher parity, gravidity, and live births were associated with decreased risk of lung cancer, which is consistent with all other Asian studies [23,25,27]. Parity and gravidity take into consideration the effect by miscarriage, abortion, stillbirth, and live birth. They cause an estrogen surge and accumulation for a period of time and reduce the number of ovulatory cycles. Our study was the first to report an increased risk associated with increased number of ovulatory cycles, supporting the hypothesis that regular dynamics of estrogen during normal ovulatory cycles, rather than accumulative endogenous or exogenous estrogen exposure, might increase the risk of lung cancer.

It has long been believed that lung cancers not related to smoking are different from those related to it [15,48]. This JFC study with post-menopausal women is the first study to report the effect modification by smoking, showing the risk smoking added to those with fewer pregnancies was greater than that added to those with more pregnancies.

Estrogen is thought to have an effect on lung cancer via estrogen receptors (ERs). Estrogen receptors α and β (ERα and ERβ), the two major types of ERs, are found in bronchial and alveolar epithelia and airway smooth muscle [14]. Both ERα and ERβ are ligand-activating transcription factors activated by 17-β estradiol (E2), the activation form of estrogen in human. The binding of E2 to ERs leads to dimerization and nuclear translocation of theses ERs. In the nucleus, ligand-bound ERα/ERβ dimers bind to the estrogen response elements (ERE) in the promoters of target genes to control cell proliferation, differentiation and apoptosis. ERs also associate with and activates EGFR (epidermal growth factor receptor, a receptor tyrosine kinase) thus triggering MAPK/ERK (mitogen-activated protein kinases/extracellular signal-regulated kinases) pathway and up/down regulating the transcription of genes that promote proliferation and invasion of lung cancer cells [49].

Strengths of this current study included homogeneity in terms of race/ethnicity, a large sample size, and a large proportion of non-smokers, which are important to reduce bias. The weak effect of menstrual and reproductive factors on lung cancer could be undetectable in a population dominated by smokers because of the strong association between smoking and lung cancer [27]. This study design also minimized selection bias by having population-based controls instead of hospital-based designs and by having very low missing rates of exposure variables of interest. In previous studies of the same topics, multiple menstrual and reproductive factors have been tested at the same time within one analysis, possibly resulting in false positive findings from multiple comparisons without correction. In our study, semi-Bayes shrinkage was applied to mitigate false positive by updating independent null priors for regression coefficients with observed data [50]. Semi-Bayes estimates were calculated also to improve the sparse data problem [42].

The weaknesses of this study included a lack of histologic categorization of lung cancer cases. The suggested association between hormonal factors and lung cancer has been identified most prominently among adenocarcinoma with EGFR mutations [45,51]. In this present study, lung cancer cases were identified from local CDC cancer registries. Due to the small proportion (20.4% cases) of lung cancer patients who had undergone surgeries or endoscope exams, there was not enough pathology or cytology information collected. Among these patients with known histology information, 65% of the NSCLC cases were adenocarcinoma. Among other studies conducted in China, lung cancer histology was largely dominated by adenocarcinoma, accounting for 61% to 73% of all female lung cancer diagnoses [22,51]. East Asian patients show a much higher prevalence of epidermal growth factor receptor (EGFR) mutations, compared with Caucasian patients with NSCLC (approximately 30% vs. 7%, predominantly among patients with adenocarcinoma and never-smokers), thus showing a higher proportion of patients who are responsive to EGFR tyrosine kinase inhibitors (EGFR-TKIs) [28,52].

Secondly, there could be recall biases brought by the case–control study design. However, all lung cancer cases were diagnosed within 1 year of interview. In addition, the study was not initially designed to test the association between hormonal factors and lung cancer and the participants were never told so. Therefore, their recalls for their exposure information were relatively objective representations of their usual life before the diagnosis of lung cancer and the recall bias has been reduced to minimum. Lastly, the sample size in the interaction study was relatively small for some of the levels of the interacting factors. We were not able to verify the causal interaction between smoking status and those menstrual and reproductive factors.

Conclusion

For postmenopausal Asian women, later menopause, more lifetime ovulatory cycles, and fewer pregnancies were associated with increased risk of lung cancer. This incremental risk appeared larger among ever smokers than their never-smoking counterparts. The potential etiological clues of estrogen in the occurrence of lung cancer need to be further explored by more epidemiologic studies with biomarkers measurements. The identification of relationships between hormonal factors and the risk of lung cancer could inform preventive strategies and therapeutic regimes. Although causal interaction was not verified, the effect modification by smoking status could potentially add rationale to tobacco smoking cessation interventions among certain female populations.

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References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, and Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* **68**, 394–424.

[2] WHO International Agency for Research on Cancer (2018). GLOBOCAN 2018 China Fact Sheet; 2018 .

[3] Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Niksic M, Bonaventure A, Valkov M, Johnson CJ, and Esteve J, et al (2018). Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet* **391**, 1023–1075.

[4] Siegel RL, Miller KD, and Jemal A (2016). Cancer statistics, 2016. *CA Cancer J Clin* **66**(1), 7–30.

[5] American Cancer Society (2017). Non-Small Cell Lung Cancer Risk Factors; 2017 .

[6] Simonato L, Agudo A, Ahrens W, Benhamou E, Benhamou S, Boffetta P, Brennan P, Darby SC, Forastiere F, and Fortes C, et al (2001). Lung cancer and cigarette smoking in Europe: an update of risk estimates and an assessment of inter-country heterogeneity. *Int J Cancer* **91**(6), 876–887.

[7] Pesch B, Kendzia B, Gustavsson P, Jockel KH, Johnen G, Pohlabeln H, Olsson A, Ahrens W, Gross IM, and Bruske I, et al (2012). Cigarette smoking and lung cancer–relative risk estimates for the major histological types from a pooled analysis of case-control studies. *Int J Cancer* **131**(5), 1210–1219.

[8] Agudo A, Ahrens W, Benhamou E, Benhamou S, Boffetta P, Darby SC, Forastiere F, Fortes C, Gaborieau V, and Gonzalez CA, et al (2000). Lung cancer and cigarette smoking in women: a multicenter case-control study in Europe. *Int J Cancer* **88**(5), 820–827.

[9] Kim CH, Lee YC, Hung RJ, McNallan SR, Cote ML, Lim WY, Chang SC, Kim JH, Ugolini D, and Chen Y, et al (2014). Exposure to secondhand tobacco smoke and lung cancer by histological type: a pooled analysis of the International Lung Cancer Consortium (ILCCO). *Int J Cancer* **135**(8), 1918–1930.

[10] Meyers TJ, Chang SC, Chang PY, Morgenstern H, Tashkin DP, Rao JY, Cozen W, Mack TM, and Zhang ZF (2017). Case-control study of cumulative cigarette tar exposure and lung and upper aerodigestive tract cancers. *Int J Cancer* **140**(9), 2040–2050.

[11] Stewart BW, WC, editors. World Cancer Report, International Agency for Research on Cancer, Lyon; 2014.

[12] American Cancer Society (2017.). Key Statistics for Small Cell Lung Cancer; 2017.

[13] Visbal AL, Williams BA, Nichols FC, Marks RS, Jett JR, Aubry MC, Edell ES, Wampfler JA, Molina JR, and Yang P (2004). Gender differences in non-small-cell lung cancer survival: An analysis of 4,618 patients diagnosed between 1997 and 2002. *Ann Thorac Surg* **78**(1), 209–215.

[14] Belani CP, Marts S, Schiller J, and Socinski MA (2007). Women and lung cancer: epidemiology, tumor biology, and emerging trends in clinical research. *Lung Cancer* **55**(1), 15–23.

[15] Couraud S, Zalcman G, Milleron B, Morin F, and Souquet PJ (2012). Lung cancer in never smokers–a review. *Eur J Cancer* **48**(9), 1299–1311.

[16] Shigematsu H, Lin L, Takahashi T, Nomura M, Suzuki M, Wistuba II, Fong KM, Lee H, Toyooka S, and Shimizu N, et al (2005). Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J Natl Cancer Inst* **97**(5), 339–346.

[17] Mollerup S, Berge G, Baera R, Skaug V, Hewer A, Phillips DH, Stangeland L, and Haugen A (2006). Sex differences in risk of lung cancer: Expression of genes in the PAH bioactivation pathway in relation to smoking and bulky DNA adducts. *Int J Cancer* **119**(4), 741–744.

[18] Miller K (2003). Estrogen and DNA damage: The silent source of breast cancer? *J Natl Cancer Inst* **95**(2), 100–102.

[19] RF Service (1998). New Role for Estrogen in Cancer? *Science* **279**(5357), 1631–1633.

[20] Ben Khedher S, Neri M, Papadopoulos A, Christiani DC, Diao N, Harris CC, Olivo-Marston S, Schwartz AG, Cote M, and Koushik A, et al (2017). Menstrual and reproductive factors and lung cancer risk: A pooled analysis from the international lung cancer consortium. *Int J Cancer* .

[21] Pesatori AC, Carugno M, Consonni D, Hung RJ, Papadoupolos A, Landi MT, Brenner H, Muller H, Harris CC, and Duell EJ, et al (2013). Hormone use and risk for lung cancer: a pooled analysis from the International Lung Cancer Consortium (ILCCO). *Brit J Cancer* **109**(7), 1954–1964.

[22] He F, Xie JX, Liu CL, WM Xiong QP Xu, Liu ZQ, Lin T, Xiao RD, Li X, and Cai L (2017). The relationship of lung cancer with menstrual and reproductive factors may be influenced by passive smoking, cooking oil fumes, and tea intake: A case-control study in Chinese women. *Medicine (Baltimore)* **96**(46), e8816.

[23] Tan HS, Tan MH, Chow KY, Chay WY, and Lim WY (2015). Reproductive factors and lung cancer risk among women in the Singapore Breast Cancer Screening Project. *Lung Cancer* **90**(3), 499–508.

[24] Schwartz AG, Ray RM, Cote ML, Abrams J, Sokol RJ, Hendrix SL, Chen C, Chlebowski RT, Hubbell FA, and Kooperberg C, et al (2015). Hormone Use, Reproductive History, and Risk of Lung Cancer: The Women's Health Initiative Studies. *J Thorac Oncol* **10**(7), 1004–1013.

[25] Gallagher LG, Rosenblatt KA, Ray RM, Li W, Gao DL, Applebaum KM, Checkoway H, and Thomas DB (2013). Reproductive factors and risk of lung cancer in female textile workers in Shanghai, China. *Cancer Causes Control* **24**(7), 1305–1314.

[26] Zhang Y, Yin Z, Shen L, Wan Y, and Zhou B (2012). Menstrual factors, reproductive factors and lung cancer risk: a meta-analysis. *Zhongguo Fei Ai Za Zhi* **15**(12), 701–719.

[27] Lim WY, Chen Y, Chuah KL, Eng P, Leong SS, Lim E, Lim TK, Ng A, Poh WT, and Tee A, et al (2012). Female reproductive factors, gene polymorphisms in the estrogen metabolism pathway, and risk of lung cancer in Chinese women. *Am J Epidemiol* **175**(6), 492–503.

[28] Zhou W and Christiani DC (2011). East meets West: ethnic differences in epidemiology and clinical behaviors of lung cancer between East Asians and Caucasians. *Chin J Cancer* **30**(5), 287–292.

[29] Zhao JK, Wu M, Kim CH, Jin ZY, Zhou JY, Han RQ, Yang J, Zhang XF, Wang XS, and Liu AM, et al (2016). Four Cancers Study: a large case-control study of lung, liver, stomach, and esophageal cancers in Jiangsu Province, China. *Eur J Cancer Prev* **26**, 357–364.

[30] Cui J, Shen Y, and Li R (2013). Estrogen synthesis and signaling pathways during aging: from periphery to brain. *Trends Mol Med* **19**(3), 197–209.

[31] Simpson ER (2003). Sources of estrogen and their importance. *J Steroid Biochem Mol Biol* **86**(3–5), 225–230.

[32] Mu LN, Lu QY, Yu SZ, Jiang QW, Cao W, You NC, Setiawan VW, Zhou XF, Ding BG, and Wang RH, et al (2005). Green tea drinking and multigenetic index on the risk of stomach cancer in a Chinese population. *Int J Cancer* **116**(6), 972–983.

[33] Lyu Y, Mirea L, Yang J, Warre R, Zhang J, Lee SK, and Li Z (2014). Secular trends in age at menarche among women born between 1955 and 1985 in Southeastern China. *BMC Womens Health* **14**, 155.

[34] Lewington S, Li L, Murugasen S, Hong LS, Yang L, Guo Y, Bian Z, Collins R, Chen J, and He H, et al (2014). Temporal trends of main reproductive characteristics in ten urban and rural regions of China: the China Kadoorie biobank study of 300 000 women. *Int J Epidemiol* **43**(4), 1252–1262.

[35] Pukelsheim F (1994). The Three Sigma Rule. *Am Stat* **48**(2), 88–91.

[36] Patient.info (2017.). Gravidity and Parity Definitions (and their Implications in Risk Assessment); 2017.

[37] Braganza MZ, de Gonzalez AB, Schonfeld SJ, Wentzensen N, Brenner AV, and Kitahara CM (2014). Benign Breast and Gynecologic Conditions, Reproductive and Hormonal Factors, and Risk of Thyroid Cancer. *Cancer Prev Res* **7**(4), 418–425.

[38] M Chavez-MacGregor SG, Elias NC, Onland-Moret YT, van der Schouw CH, Van Gils E, Monninkhof DE, Grobbee PH, and Peeters (2005). Postmenopausal breast cancer risk and cumulative number of menstrual cycles. *Cancer Epidemiol Biomark Prev* **14**(4), 799–804.

[39] Zhou B (2002). C Coorperative Meta-Analysis Group Of Working Group On Obesity In, [Prospective study for cut-off points of body mass index in Chinese adults]. *Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi* **23**(6), 431–434.

[40] Yu M, Rao K, and Chen Y (2000). A case-control study of the risk factors of lung cancer in Beijing, Tianjin, Shanghai, Chongqing metropolitan areas. *Zhonghua yu fang yi xue za zhi [Chinese journal of preventive medicine]* **34**(4), 227–231.

[41] ZY Jin M Wu, Han RQ, Zhang XF, Wang XS, Liu AM, JY Zhou QY Lu, and CH Kim LN Mu, et al (2014). Household Ventilation May Reduce Effects of Indoor Air Pollutants for Prevention of Lung Cancer: A Case-Control Study in a Chinese Population. *PLoS One* **9**(7).

[42] Greenland S (2007). Bayesian perspectives for epidemiological research. II. Regression analysis. *Int J Epidemiol* **36**(1), 195–202.

[43] Odongkara Mpora B, Piloya T, Awor S, Ngwiri T, Laigong P, Mworozi EA, and Hochberg Z (2014). Age at menarche in relation to nutritional status and critical life events among rural and urban secondary school girls in post-conflict northern Uganda. *BMC Womens Health* **14**, 66.

[44] Rogers IS, Northstone K, Dunger DB, Cooper AR, Ness AR, and Emmett PM (2010). Diet throughout childhood and age at menarche in a contemporary cohort of British girls. *Public Health Nutr* **13**(12), 2052–2063.

[45] Weiss JM, Lacey Jr JV, Shu XO, Ji BT, Hou L, Yang G, Li H, Rothman N, Blair A, and Gao YT, et al (2008). Menstrual and reproductive factors in association with lung cancer in female lifetime nonsmokers. *Am J Epidemiol* **168**(11), 1319–1325.

[46] Seow A, Koh WP, Wang RW, Lee MC, and Yu MC (2009). Reproductive Variables, Soy Intake, and Lung Cancer Risk among Nonsmoking Women in the Singapore Chinese Health Study. *Cancer Epidem Biomar* **18**(3), 821–827.

[47] Wuwilliams AH, Dai XD, Blot W, Xu ZY, Sun XW, Xiao HP, Stone BJ, Yu SF, Feng YP, and Ershow AG, et al (1990). Lung-Cancer among Women in North-East China. *Br J Cancer* **62**(6), 982–987.

[48] Sun S, Schiller JH, and Gazdar AF (2007). Lung cancer in never smokers–a different disease. *Nat Rev Cancer* **7**(10), 778–790.

[49] Chakraborty S, Ganti AK, Marr A, and Batra SK (2010). Lung cancer in women: role of estrogens. *Expert Rev Respir Med* **4**(4), 509–518.

[50] Greenland S (2008). Multiple comparisons and association selection in general epidemiology. *Int J Epidemiol* **37**(3), 430–434.

[51] Gao YT, Blot WJ, Zheng W, Ershow AG, Cheng WH, Levin LI, Rong Z, and Fraumeni JF (1987). Lung-Cancer among Chinese-Women. *Int J Cancer* **40**(5), 604–609.

[52] Qin BM, Chen X, Zhu JD, and Pei DQ (2005). Identification of EGFR kinase domain mutations among lung cancer patients in China: implication for targeted cancer therapy. *Cell Res* **15**(3), 212–217.