Menstrual factors, reproductive history, and risk of lung cancer: a multi-center population-based cohort study in Chinese females

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Background: Female menstrual and reproductive factors, as remarkable indicators of hormone effect, were hypothesized to be associated with lung cancer risk, whereas the existed epidemiological evidence was inconsistent. Our study aims to investigate the association between menstrual and reproductive factors and lung cancer risk based on the Chinese Lung Cancer Screening Program.

Methods: This study was based on a large-scale multi-center population cohort across China recruiting individuals aged 40–74 years old between 2013–2018. Cox regression model was applied to estimate the HRs and 95% CIs. Restricted cubic spline (RCS) analysis was used to estimate dose-response relationships and test for nonlinear associations.

Results: Among 553,434 female participants, 1,529 incident lung cancer cases were identified with a median follow-up of 3.61 years. With adjustment for multiple covariates and all significant hormonal factors, elevated lung cancer risk was associated with later age (15, or ≥16 years) at menarche (HR =1.27, 95% CI:

1.04–1.56; HR =1.45, 95% CI: 1.19–1.76), later age (25–29, or ≥30 years) at first live birth (HR =1.27, 95% CI: 1.13–1.43; HR =1.23, 95% CI: 1.00–1.51), and benign breast disease history (HR =1.25, 95% CI: 1.10-1.41). For postmenopausal females specifically, surgical menopause (HR =1.62; 95% CI: 1.29–2.05) and other surgeries on the reproductive system (HR =1.19; 95% CI: 1.01–1.40) both appeared to be predictive of elevated lung cancer risk. Concerning age at menopause, a nonlinear association was observed (P-nonlinear =0.0126). Increased lung cancer risk was observed among females with age at menopause especially above 50. Although we observed no significant associations between longer time (≥13 months) of breastfeeding and lung cancer risk among all participants (HR =0.86; 95% CI: 0.71–1.04), significant decreased adenocarcinoma risk (HR =0.65; 95% CI: 0.53–0.81) was noted among nonsmoking females.

Conclusions: Our findings add some support for the role of menstrual and reproductive factors in lung carcinogenesis. However, these relationships were complex, and required further investigations addressing the biological mechanisms.

Keywords: Lung cancer; hormones; population-based; cohort study.

Introduction

Lung cancer remains the leading cause of cancer deaths worldwide. In 2020, more than one-third of lung cancer cases and deaths occurred in China (1). From 2000 to 2015, the female lung cancer incidence rate doubled in China $(57.26/10^5$ *vs.* $27.77/10^5)$ (2) with an average annual change percentage (AACP) of 4.5% (3).

Smoking is the leading risk factor for lung cancer and is linked to over 80% of lung cancers worldwide (4). In China, 75.04% of lung cancer deaths were attributable to tobacco smoking in males, whereas only 18.35% of lung cancer deaths in females were attributed to active smoking (5). There were still two-thirds of female lung cancer associated with unidentified risk factors besides active smoking, involuntary smoking, occupational agents, indoor radon and low fruit intake (5). Accumulating evidence suggests that female lung cancers differed from lung cancer in males concerning the clinical characteristic (6). Female lung cancers are mainly composed of adenocarcinoma (7) and have a higher frequency of epidermal growth factor receptor (EGFR) mutations compared with male lung cancer cases (8). These literatures suggested that gender differences in clinical characteristics may underlie the effect of hormone-related factors.

Experimental studies showed that steroid hormone-related receptors including estrogen receptors are frequently expressed in lung cancer tissue (9). By binding to estrogen receptors α (ERα), estrogen may promote cell proliferation or decreasing apoptosis through activating target genes (10-13). Therefore, estrogen is postulated as an important agent in female cancer development (14).

Menstrual factors and reproductive history, which are remarkable indicators of endogenous hormonal effect, have been widely explored in epidemiological studies (15-33). However, inconsistent associations have been suggested (15-19,21,23,26,29,32). Therefore, we conducted a meta-analysis of worldwide studies on endogenous sex steroid hormone (34). Though overall results showed that higher levels of sex steroid hormones were associated with decreased female lung cancer risk, Asian studies revealed quite different associations concerning the age at menopause, age at first live birth, and reproductive window, compared with Western studies. For the Asian population, cohort studies in Japan, Singapore and China (19,22,23) have reported significant associations with age at menarche and menopause, reproductive period, live birth history, and reproductive surgical history. However, multi-center cohort studies with the estimation of lung adenocarcinoma risk are lacking in Chinese females (25-27).

This study aims to investigate the association between reproductive factors and risk of lung cancer and specifically, risk of adenocarcinoma, among Chinese females in a multi-center population cohort. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/tlcr-21-552).

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Methods

Study design and population

We conducted a multi-center prospective cohort study based on the Chinese lung cancer screening program, a non-profit program launched in 2012 and funded by the Ministry of Finance and the National Health Commission of China. Participants were eligible if they were asymptomatic of lung cancer, had no history of any cancer types, and aged between 40–74 years. Eligible participants who provided written informed consent were interviewed by trained staff to collect information about their exposure to risk factors. Then, their lung cancer risks were evaluated using an established risk score system. Individuals who were defined as high-risk for lung cancer were recommended to undergo a free LDCT examination at a tertiary-level hospital designated by the program.

Eight study provinces (Anhui, Beijing, Guangxi, Henan, Hunan, Jiangsu, Liaoning, and Zhejiang province) were selected for our study based on the following criteria: (I) complete cancer registration data, (II) complete vital statistics data, (III) cross-reference medical records from hospital information systems, and (IV) minor migration representing a relatively stable population. Between 2013–2018, there were 1,016,740 eligible participants recruited in the Chinese lung cancer screening program, among which 570,713 were females. Eventually, a total of 553,434 females with valid information concerning the age at menarche (8–18 years), menopause (30–60 years), and first live birth (18–45 years) were included in the study (*Figure 1*).

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of China National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (number of IRB:15-070/997). Informed consent was taken from all individual participants.

Exposure assessment

Potential lung cancer risk factors except for height and weight were collected by self-report questionnaire at baseline entry. Menstrual factors include age at menarche (<13, 13, 14, 15, or ≥16, years), menopause status of the postmenopausal females (natural menopause or surgical menopause, surgical menopause was defined as

menopause caused by surgeries including hysterectomy and oophorectomy, natural menopause was defined as menopause caused by the natural aging process without surgical intervention), age at menopause (<45, 45–49, 50–54 or ≥55, years) and reproductive period (time between menarche and menopause, <30, 30–34, 35–39 or ≥40, years). The reproductive history contained age at first live birth (nulliparous, <25, 25–29, or ≥30, years), duration of breastfeeding (0, 1–12, or ≥13, months), benign breast disease history (mainly including breast fibroma and cystic hyperplasia) and surgical history on the reproductive system (surgeries other than hysterectomy and oophorectomy, mainly including tubal ligation, cesarean section, and myomectomy of the uterus).

Eight provinces were classified as developed areas (Beijing, Zhejiang, and Jiangsu Provinces) or developing areas (Anhui, Hunan, Liaoning, Guangxi, and Henan Provinces) based on each province's per capita gross domestic product (GDP) values in 2018. Marital status was defined as married or other (including unmarried, divorced, or widowed). Education level was defined in three categories, low (less than elementary school), medium (junior or high school or equivalent), and high (college degree equivalent or higher). Height and weight measured wearing light clothes without shoes were used to calculate the body-mass index (BMI), which was divided into 4 categories according to the Chinese standard: underweight (<18.5 kg/m^2), normal (18.5–23.9 kg/m^2), overweight (24.0–27.9 kg/m^2) or obese (≥28.0 kg/m^2). Smoking status was classified as current (>1 cigarette/day for at least 6 months), former (previously smoked and have quit for at least 6 months), and never-smokers (those who reported neither current smoking status nor smoking history). Exposures to environmental tobacco smoke (yes or no) referred to exposure to tobacco combustion products from smoking by indoor regular smokers (>1 cigarette/day for at least 6 months) in both workplace and living place. Exposures to cooking smoke were categorized as 'none (0 h/day)', 'little (0–1 h/day)', 'some (1–4 h/day)', 'much (>4 h/day)' by self-report. Occupational exposures referred to the exposures to either one of asbestos, rubber, dust, pesticide, radiation, beryllium, uranium, and radon for at least one year. History of chronic respiratory disease (yes or no) referred to previous clinical diagnoses of pulmonary tuberculosis, chronic bronchitis, emphysema, asthmatic bronchiectasis, silicosis, and pneumoconiosis, etc. Family history of lung cancer (yes or no) referred to previous clinical diagnosis of
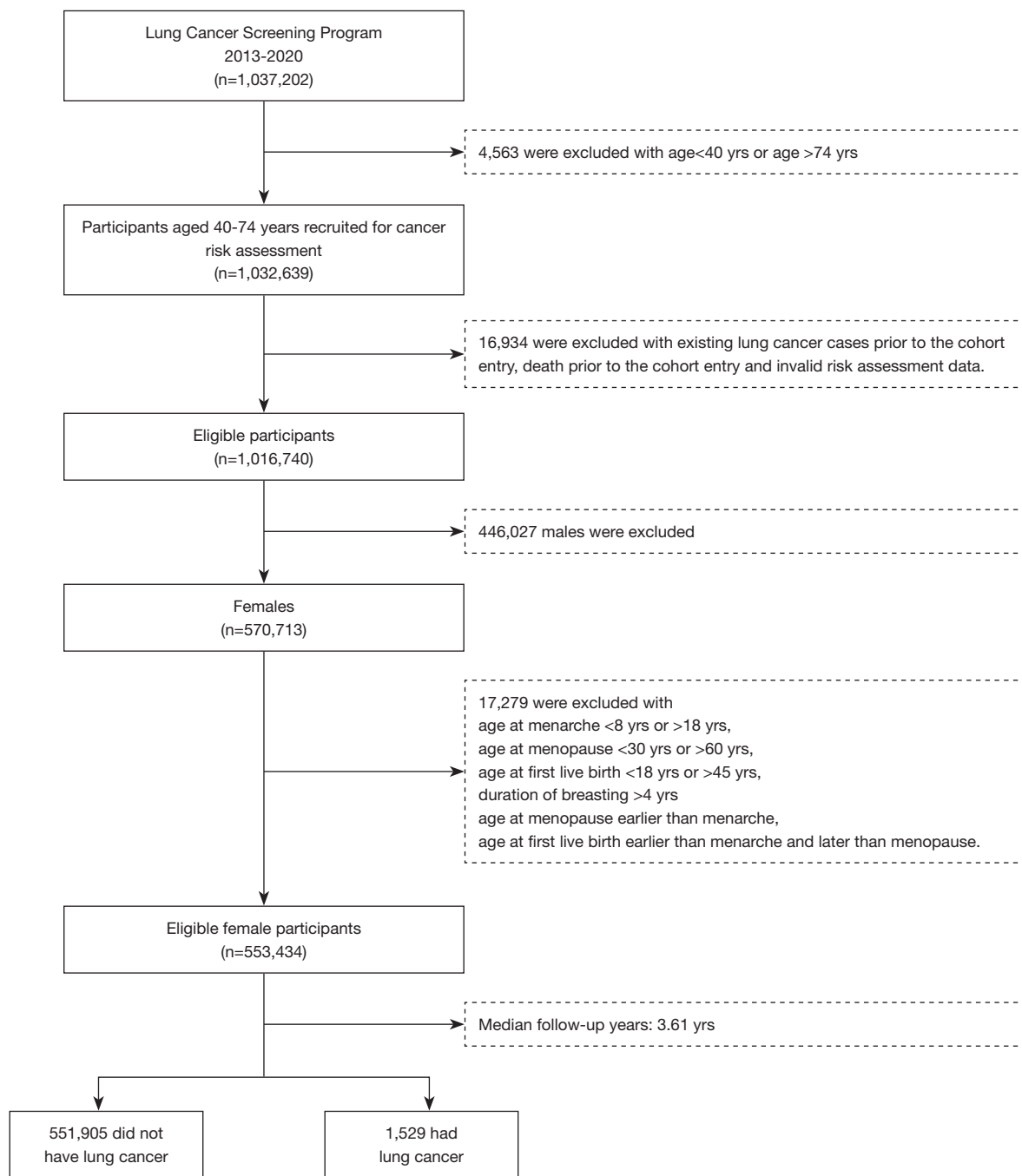
Figure 1 Workflow of the Chinese Lung Cancer Screening Program. yrs, years.

cancer among participants' first-degree relatives.

Follow-up of participants

Follow-up of each participant began when the baseline questionnaire was finished and ended at first diagnosis of lung cancer, death, last documented follow-up contact, or 20th June 2020, whichever came first. We linked the system of our program to the cancer registry system and death surveillance system to obtain information on lung cancer incidence. The information was also cross-referenced with records from the medical insurance system and local

hospitals. All cancer cases were classified according to the International Classification standards (ICD-10), in which lung cancer was coded as C34.

Quality control

A clinical expert committee consisting of thoracic surgeons, radiologists, and pathologists was formed to assure the accuracy of lung cancer diagnoses. Identified lung cancer cases, as well as their clinical stage and histological type, were cross-referenced with the cancer registration system, vital statistics data, health insurance system, and medical records. Overall, 94.0% of lung cancer cases were matched across databases. For the remaining cases with unsuccessful linkages, telephone interviews were further constructed to verify the information of lung cancer cases and deaths.

Statistical analysis

The baseline questionnaire data and information on lung cancer cases were used in the analysis. Continuous variables are presented as the mean ± standard deviation (SD) and compared using t-tests. Categorical variables were described by proportions and compared using Chi-square tests.

The risk of developing lung cancer in relationship to baseline menstrual and reproductive factors was evaluated using Cox regression models. Each reproductive factor was modeled separately in relation to disease outcome. Notably, menopause status (natural or surgical menopause) and age at menopause were evaluated among postmenopausal females only. Estimation of hazard ratios (HRs) and 95% confidence intervals (CIs) was conducted with adjustment of covariates including age at enrollment (continuous), education (low, medium, or high), BMI (underweight, normal, overweight or obese), smoking status (current, former or never-smoker), exposures to environmental tobacco smoke (yes or no), exposure to cooking smoke (none, little, some, or much), occupational exposures (yes or no), history of chronic respiratory disease (yes or no) and family history of lung cancer (yes or no). Considering the within-cluster correlation of different provinces, a shared frailty model was used, in which cluster effects of the province are incorporated into the model as independent and identically distributed variables.

For originally continuous variables, dose-response relationships and tests for non-linear associations were conducted using restricted cubic spline (RCS) regression with three knots (placed at the 5th, 50th, and 95th percentiles) (35). The median values were assigned as the spline referent.

Moreover, associations were further investigated in multivariable models among all recruited females and postmenopausal females only. The final multivariable models contain statistically significant risk factors including age at menarche, age at first live birth, duration of breastfeeding, benign breast disease, surgery on the reproductive system, menopause status and age at menopause (the last two for postmenopausal females only). Considering the low smoking prevalence of our participants, sensitivity analyses were further conducted among never-smokers.

Tests in this study were all two-sided and P<0.05 was considered statistically significant. All statistical analyses were conducted using the SAS statistical software, version 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

During a median follow-up of 3.61 years, 553,434 females were diagnosed with 1529 lung cancer, for an incidence density of $75.19/10^5$ person-years. (*Figure 1*). Baseline characteristics of the study population stratified by lung cancer status were presented in *Table 1*. The mean age of recruited participants was 55.76±8.64 years, with 95.73% never-smokers and 37.70% passive smokers. Adenocarcinoma was the predominant histology type of lung cancer cases, accounting for 91.20%.

Compared with the non-case group, lung cancer patients were older (59.72±7.48 vs. 55.75±8.64 years), and had a higher prevalence of passive smoking (41.14% vs. 37.69%), chronic respiratory diseases (26.29% vs. 20.43%) and family history of lung cancer (17.72% vs. 11.67%). With respect to reproductive factors, lung cancer patients were at a later age of menarche (14.63±1.67 vs. 14.27±1.61 years), first live birth (25.23±4.66 vs. 24.85±4.70 years) and menopause (49.69±3.36 vs. 49.41±3.17 years), reported shorter time of breastfeeding (12.31±7.98 vs. 12.46±8.68 months), and had a higher proportion of benign breast disease history (35.32% vs. 31.44%).

After adjustment for multiple covariates (detailed in "Statistical Analysis" and footnote of *Table 2*), the associations between reproductive factors and lung cancer risk overall, and adenocarcinoma specifically, were listed in *Table 2*. Increased lung cancer risk was associated with later age (15, or ≥16 years) at menarche (vs. 13 years: HR =1.26, 95% CI: 1.03–1.54; HR =1.43, 95% CI: 1.17–1.73), later

Table 1 Baseline characteristics of participants by lung cancer status

Variable	Total (N=553,434)	No lung cancer (N=551,905)	Lung cancer (N=1,529)	P value
Age at enrollment, year				
Mean ± SD	55.76±8.64	55.75 ±8.64	59.72 ±7.48	<0.0001
Age, years, No (%[†])				
40–44	65,069 (11.76)	65,019 (11.78)	50 (3.27)	<0.0001
45–49	90,175 (16.29)	90,054 (16.32)	121 (7.91)	
50–54	100,597 (18.18)	100,374 (18.19)	223 (14.58)	
55–59	92,424 (16.70)	92,157 (16.70)	267 (17.46)	
60–64	98,608 (17.82)	98,217 (17.80)	391 (25.57)	
65–69	79,537 (14.37)	79,152 (14.34)	385 (25.18)	
70–74	27,024 (4.88)	26,932 (4.88)	92 (6.02)	
Education, No (%[†])				
Low	111,671 (20.18)	111,306 (20.17)	365 (23.87)	0.0005
Medium	360,648 (65.17)	359,717 (65.18)	931 (60.89)	
High	81,115 (14.66)	80,882 (14.66)	233 (15.24)	
Marital status, No (%[†])				
Married	516,099 (93.25)	514,686 (93.26)	1,413 (92.41)	0.1894
Other	37,335 (6.75)	37,219 (6.74)	116 (7.59)	
Economic region, No (%[†])				
Developed areas	192,562 (34.79)	192,056 (34.80)	506 (33.09)	0.1621
Developing areas	360,872 (65.21)	359,849 (65.20)	1,023 (66.91)	
Smoking status, No (%[†])				
Never	529,823 (95.73)	528,369 (95.74)	1,454 (95.09)	0.4576
Current	19,986 (3.61)	19,922 (3.61)	64 (4.19)	
Former	3,625 (0.66)	3,614 (0.65)	11 (0.72)	
Environmental tobacco smoke, No (%[†])				
No	344,791 (62.30)	343,891 (62.31)	900 (58.86)	0.0055
Yes	208,643 (37.70)	208,014 (37.69)	629 (41.14)	
Exposure to cooking smoke, No (%[†])				
None	66,836 (12.08)	66,668 (12.08)	168 (10.99)	0.6072
Little	397,183 (71.77)	396,069 (71.76)	1,114 (72.86)	
Some	71,578 (12.93)	71,382 (12.93)	196 (12.82)	
Much	17,837 (3.22)	17,786 (3.22)	51 (3.34)	
Occupational exposure, No (%[†])				
No	463,002 (83.66)	461,738 (83.66)	1,264 (82.67)	0.2937
Yes	90,432 (16.34)	90,167 (16.34)	265 (17.33)	

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Total (N=553,434)	No lung cancer (N=551,905)	Lung cancer (N=1,529)	P value
BMI[‡], No (%[†])				
Underweight	12,083 (2.18)	12,047 (2.18)	36 (2.35)	0. 7604
Normal	303,311 (54.81)	302,490 (54.81)	821 (53.70)	
Overweight	190,799 (34.48)	190,266 (34.47)	533 (34.86)	
Obese	47,241 (8.54)	47,102 (8.53)	139 (9.09)	
Family history of lung cancer, No (%[†])				
No	488,776 (88.32)	487,518 (88.33)	1,258 (82.28)	<0.0001
Yes	64,658 (11.68)	64,387 (11.67)	271 (17.72)	
History of chronic respiratory diseases, No (%[†])				
No	440,291 (79.56)	439,164 (79.57)	1,127 (73.71)	<0.0001
Yes	113,143 (20.44)	112,741 (20.43)	402 (26.29)	
Age at menarche, year				
Mean ± SD	14.27±1.61	14.27±1.61	14.63±1.67	<0.0001
<13	68,602 (12.40)	68,465 (12.41)	137 (8.96)	<0.0001
13	113,617 (20.53)	113,348 (20.54)	269 (17.59)	
14	145,319 (26.26)	144,956 (26.26)	363 (23.74)	
15	105,217 (19.01)	104,906 (19.01)	311 (20.34)	
≥16	120,679 (21.81)	120,230 (21.78)	449 (29.37)	
Menopause status[‡], No (%[†])				
Natural menopause	350,273 (63.29)	349,073 (63.25)	1,200 (78.48)	<0.0001
Surgical menopause	14,492 (2.62)	14,411 (2.61)	81 (5.30)	
Age at menopause[‡], year				
Mean ± SD	49.41±3.17	49.41±3.17	49.69±3.36	0.0028
<45	20,636 (5.66)	20,558 (5.66)	78 (6.09)	<0.0001
45–49	126,294 (34.62)	125,909 (34.64)	385 (30.05)	
50–54	200,368 (54.93)	199,631 (54.92)	737 (57.53)	
≥55	17,467 (4.79)	17,386 (4.78)	81 (6.32)	
Reproductive period[‡], year				
Mean ± SD	34.98±3.50	34.98±3.49	34.98±3.61	0.9929
<30	23,099 (6.33)	23,007 (6.33)	92 (7.18)	<0.0001
30–34	116,577 (31.96)	116,175 (31.96)	402 (31.38)	
35–39	199,028 (54.56)	198,338 (54.57)	690 (53.86)	
≥40	26,061 (7.14)	25,964 (7.14)	97 (7.57)	

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Total (N=553,434)	No lung cancer (N=551,905)	Lung cancer (N=1,529)	P value
Age at first live birth, year				
Mean ± SD	24.85±4.70	24.85±4.70	25.23±4.66	0.0015
Nulliparous	12,642 (2.28)	12,611 (2.28)	31 (2.03)	<0.0001
<25	200,009 (36.14)	199,540 (36.15)	469 (30.67)	
25–29	303,569 (54.85)	302,668 (54.84)	901 (58.93)	
≥30	37,214 (6.72)	37,086 (6.72)	128 (8.37)	
Duration of breastfeeding, month				
Mean ± SD	12.46±8.68	12.46±8.68	12.31±7.98	<0.0001
0	60,885 (11.00)	60,694 (11.00)	191 (12.49)	<0.0001
1–12	322,508 (58.27)	321,545 (58.26)	963 (62.98)	
≥13	170,041 (30.72)	169,666 (30.74)	375 (24.53)	
Benign breast disease, No (%[†])				
No	379,377 (68.55)	378,388 (68.56)	989 (64.68)	0.0011
Yes	174,057 (31.45)	173,517 (31.44)	540 (35.32)	
Surgeries on the reproductive system, No (%[†])				
No	474,009 (85.65)	472,716 (85.65)	1,293 (84.57)	0.2262
Yes	79,425 (14.35)	79,189 (14.35)	236 (15.43)	
Histology type[§]				
Adenocarcinoma	NA	NA	1,202 (91.20)	NA
Squamous cell carcinomas	NA	NA	55 (4.17)	
Small-cell carcinoma	NA	NA	36 (2.73)	
Others	NA	NA	236 (1.90)	

[†], column percentage; [‡], among postmenopausal women only; [§], 211 lung cancer cases without information on histological type. SD, standard derivation; BMI, body-mass index.

age (25–29, or ≥30 years) at first live birth (*vs.* <25 year: HR =1.31, 95% CI: 1.17–1.47; HR =1.31, 95% CI: 1.07–1.60), benign breast disease history (HR =1.27, 95% CI: 1.13–1.44) and reproductive system surgical history (HR =1.15; 95% CI: 1.00–1.33). Decreased lung cancer risk was associated with a longer time (≥13 months) of breastfeeding (*vs.* no breastfeeding: HR =0.82; 95% CI: 0.69–0.98). Among postmenopausal females, those who experienced surgical menopause were at increased lung cancer risk (HR =1.64; 95% CI: 1.31–2.06). As for adenocarcinoma specifically, similar risk estimates were noted compared with overall lung cancer risk. Additionally, normal (45–49, or 50–54) age at menopause

was associated with decreased lung adenocarcinoma risk (*vs.* <45 years: HR =1.64; 95% CI: 1.31–2.06). The association concerning surgery on the reproductive system converted to be insignificant.

Figure 2 presented the dose-response associations between reproductive factors and lung cancer risk. Significant nonlinear association was only suggested concerning the age at menopause (P-overall =0.0160, P-nonlinear =0.0126). Lung cancer risks increased with age at menopause above 50 or below 45, somehow the association was insignificant concerning menopause age younger than 45. Age at menarche (P-overall <0.0001, P-nonlinear =0.6486), time of breastfeeding

Table 2 Risk of developing lung cancer in relationship to baseline menstrual and reproductive factors

Factors	Lung cancer		Adenocarcinoma	
	Cases (N=1,529)	HR[†] (95% CI)	Cases (N=1,202)	HR[†] (95% CI)
Age at menarche, year				
<13	137	Ref	107	Ref
13	269	1.12 (0.91–1.37)	207	1.11 (0.88–1.40)
14	363	1.13 (0.92–1.37)	275	1.11 (0.88–1.39)
15	311	1.26 (1.03–1.54)	254	1.33 (1.06–1.68)
≥16	449	1.43 (1.17–1.73)	359	1.49 (1.20–1.86)
Menopause status[‡]				
Natural menopause	1,200	Ref	921	Ref
Surgical menopause	81	1.64 (1.31–2.06)	72	1.85 (1.45–2.35)
Age at menopause[‡], year				
<45	78	Ref	68	Ref
45–49	385	0.78 (0.61–1.00)	301	0.71 (0.55–0.93)
50–54	737	0.86 (0.68–1.08)	561	0.76 (0.59–0.98)
≥55	81	0.95 (0.69–1.29)	63	0.86 (0.61–1.22)
Reproductive period[‡], year				
<30	92	Ref	79	Ref
30–34	402	0.83 (0.67–1.05)	308	0.85 (0.67–1.06)
35–39	690	0.80 (0.65–1.00)	536	0.83 (0.67–1.03)
≥40	97	0.80 (0.60–1.16)	70	0.84 (0.63–1.12)
Age at first live birth, year				
Nulliparous	31	1.23 (0.85–1.77)	23	1.20 (0.78–1.83)
<25	469	Ref	345	Ref
25–29	901	1.31 (1.17–1.47)	728	1.43 (1.25–1.63)
≥30	128	1.31 (1.07–1.60)	106	1.44 (1.15–1.80)
Duration of breastfeeding, month				
0	191	Ref	154	Ref
1–12	963	0.99 (0.84–1.15)	765	0.99 (0.83–1.18)
≥13	375	0.82 (0.69–0.98)	283	0.81 (0.66–0.99)
Benign breast disease				
No	989	Ref	759	Ref
Yes	540	1.27 (1.13–1.44)	443	1.33 (1.16–1.52)
Surgery on the reproductive system				
No	1,293	Ref	1,012	Ref
Yes	236	1.15 (1.00–1.33)	190	1.15 (0.98–1.35)

[†], adjusted for age at enrollment (continuous), education (low, medium, or high), BMI (underweight, normal, overweight or obese), smoking status (current, former or never-smoker), exposures to environmental tobacco smoke (yes or no), exposure to cooking smoke (none, little, some, or much), occupational exposures (yes or no), history of chronic respiratory disease (yes or no) and family history of lung cancer (yes or no). Province of different economic region was treated as a random variable considering within-cluster correlation. [‡], among postmenopausal women only. HR, hazard ratio; CI, confidence interval.
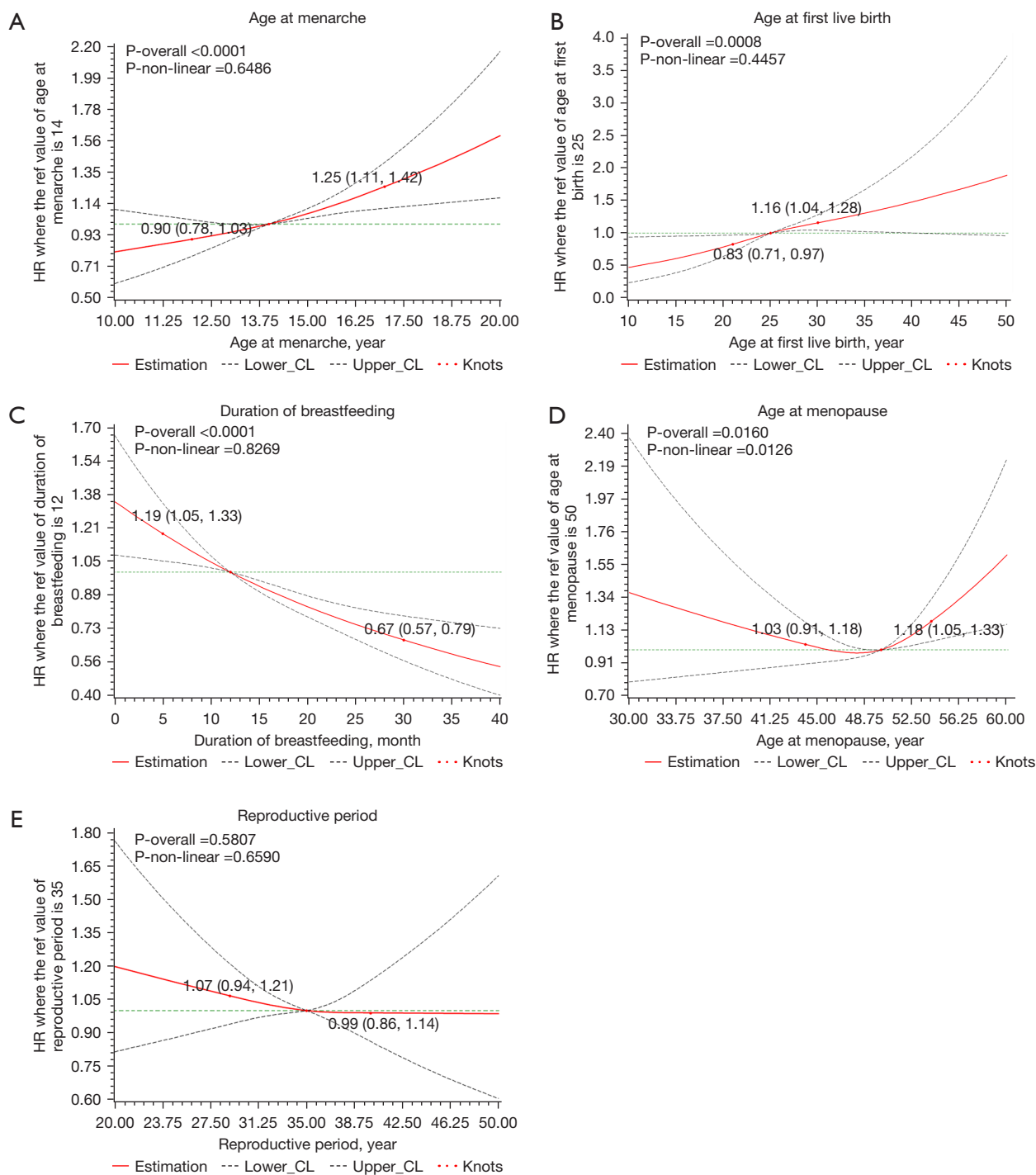
Figure 2 Cubic spline graph of the adjusted HR (represented by solid line) and 95% CI (represented by the dotted lines) for the association between menstrual and reproductive factors and lung cancer risk. (A) Age at menarche, reference: 14 years old; (B) age at first live birth, reference: 25 years old; (C) duration of breastfeeding, reference: 12 months; (D) age at menopause, reference: 50 years old; (E) reproductive period, reference: 35 years; Knots: 5th, 50th, 95th of the distribution. Analyses are adjusted for age at enrollment (continuous), education (low, medium, or high), BMI (underweight, normal, overweight or obese), smoking status (current, former or never-smoker), exposures to environmental tobacco smoke (yes or no), exposure to cooking smoke (none, little, some, or much), occupational exposures (yes or no), history of chronic respiratory disease (yes or no) and family history of lung cancer (yes or no).

(P-overall =0.0008, P-nonlinear =0.4457) and duration of breastfeeding (P-overall <0.0001, P-nonlinear =0.8269) were all approximately linearly associated with lung cancer risk. No significant association was suggested between the reproductive period and lung cancer risk (P-overall =0.5807). For lung adenocarcinoma, similar associations were also noted and displayed in Figure S1.

Adjusted for multiple covariates and all significant reproductive factors in *Table 2*, lung cancer and adenocarcinoma-specific risk among all recruited females and postmenopausal females only were further estimated in multivariable models (*Table 3*). Despite of insignificant association concerning time of breastfeeding (≥13 months *vs.* no breastfeeding: HR =0.86; 95% CI: 0.71–1.04), significant risk increases were confirmed among females with later age (15, or ≥16 years) at menarche (*vs.* <13 years: HR =1.27, 95% CI: 1.04–1.56; HR =1.45, 95% CI: 1.19–1.76), later age (25–29, or ≥30 years) at first live birth (<25 years: HR =1.27, 95% CI: 1.13–1.43; HR =1.23, 95% CI: 1.00–1.51), and benign breast disease history (HR =1.25, 95% CI: 1.10–1.41). No additional association was suggested for adenocarcinoma. Specific to postmenopausal females, those who experienced surgical menopause (HR =1.62; 95% CI: 1.29–2.05) and other surgeries on the reproductive system (HR =1.19; 95% CI: 1.01–1.40) were at significantly increased lung cancer risks. Similar risk estimates were noted for lung adenocarcinoma risk among postmenopausal females.

Sensitivity analyses among lifetime never smokers were displayed in *Table 4*. Among nonsmoking females, a longer duration of breastfeeding (≥13 months) was significantly associated with decreased overall lung cancer risk (*vs.* no breastfeeding: HR =0.82; 95% CI: 0.67–1.00), and especially adenocarcinoma risk (HR =0.65; 95% CI: 0.53–0.81).

Discussion

Based on a large-scale multi-centered cohort study of Chinese females, this analysis displayed elevated lung cancer risk among females with later age (15, or ≥16 years) at menarche, later age (25–29, or ≥30 years) at first live birth, and benign breast disease history. For postmenopausal females specifically, surgical menopause and surgical history of the reproductive system other than hysterectomy and oophorectomy both appeared to be predictive of elevated lung cancer risk. A nonlinear association was observed concerning the age at menopause, suggesting increased lung cancer risks with age at menopause below 45 and especially, above 50. Although we observed no significant associations

between longer time (≥13 months) of breastfeeding and lung cancer risk among all participants, significantly decreased adenocarcinoma risk was noted among nonsmoking females.

So far, 11 cohort studies were performed on the association between hormonal factors and lung cancer risk and yielded inconsistent results (Table S1). Notably, our study firstly addressed the associations among Chinese females with the estimation of adenocarcinoma-specific lung cancer risk based on a large-scale multi-center cohort. It is noteworthy that the restricted cubic spline analysis was also firstly applied to evaluate the nonlinear association between continuous menstrual factors and lung cancer risk.

In this analysis, we observed that later age at menarche was associated with increased lung cancer risk. Although this may suggest that the role of hormonal factors in adolescence as initiating factors for subsequent lung pathologies, it should be noted that age at menarche can be influenced by many exposures in early life which were unable to be measured in our study. Our finding corroborates the published meta-analysis (34) and especially several Chinese studies (21-23,25,26). In contrast to our findings, some studies reported a reduced lung cancer risk associated with late menarche (16,19), however, subsequent results based on the same cohort were paradoxical (18). There were also two Chinese studies (32,33) that suggested inverse associations, which provide insufficient evidence based on the case-control study design.

Consistent with several studies (17,36), we noted a similar positive association with age at first live birth. Since the self-regulating capacity in endogenous estrogen decreases as females get older, late childbirth may be more likely to cause hormonal disorders. Nonetheless, other studies also reported either non-significant (15,19,23,24,26,31) or reduced risks (16,30,33). In these studies, the categories of age at first live birth were not unified in these analyses, which might limit the comparability of these findings. Besides, a few studies have suggested decreased risks for higher parity (22,26), however, the influence of parity was not evaluated in our analysis.

We observed that benign breast disease history was positively associated with lung cancer risk. However, there was no evidence before reporting the relationship of benign breast disease to lung cancer risk. Though we considered benign breast disease as an indicator of hormonal disturbances and elevated lung cancer risk, this innovative association was plausive considering the detection signal bias. Therefore, more evidence is needed concerning this assertion.

Table 3 Multivariable model for lung cancer risk

Factors	All females recruited				Postmenopausal females			
	Lung cancer		Adenocarcinoma		Lung cancer		Adenocarcinoma	
	Cases (N=1,529)	Model a[†], HR (95% CI)	Cases (N=1,202)	Model a[†], HR (95% CI)	Cases (N=1,281)	Model b[‡], HR (95% CI)	Cases (N=993)	Model b[‡], HR (95% CI)
Menopause status								
Natural menopause					1,200	Ref	921	Ref
Surgical menopause					81	1.62 (1.29–2.05)	72	1.78 (1.39–2.29)
Age at menopause, year								
<45					78	Ref	68	Ref
45–49					385	0.86 (0.67–1.10)	301	0.80 (0.61–1.05)
50–54					737	0.94 (0.74–1.19)	561	0.85 (0.65–1.10)
≥55					81	1.00 (0.73–1.37)	63	0.92 (0.65–1.30)
Age at menarche, year								
<13	137	Ref	107	Ref	100	Ref	77	Ref
13	269	1.14 (0.92–1.40)	207	1.07 (0.84–1.36)	224	1.25 (0.98–1.58)	171	1.25 (0.96–1.64)
14	363	1.15 (0.94–1.40)	275	1.09 (0.87–1.37)	298	1.22 (0.97–1.53)	219	1.19 (0.91–1.54)
15	311	1.27 (1.04–1.56)	254	1.29 (1.02–1.63)	260	1.33 (1.05–1.68)	211	1.43 (1.10–1.86)
≥16	449	1.45 (1.19–1.76)	359	1.48 (1.19–1.86)	399	1.51 (1.21–1.89)	315	1.58 (1.23–2.03)
Age at first live birth, year								
Nulliparous	31	1.20 (0.81–1.78)	23	1.08 (0.67–1.76)	24	1.29 (0.83–2.02)	19	1.36 (0.82–2.24)
<25	469	Ref	345	Ref	413	Ref	298	Ref
25–29	901	1.27 (1.13–1.43)	728	1.40 (1.22–1.60)	744	1.20 (1.06–1.36)	593	1.31 (1.13–1.51)
≥30	128	1.23 (1.00–1.51)	106	1.32 (1.05–1.68)	100	1.15 (0.91–1.44)	83	1.27 (0.99–1.64)
Duration of breastfeeding, month								
0	191	Ref	154	Ref	155	Ref	126	Ref
1–12	963	1.02 (0.80–1.13)	765	0.99 (0.82–1.21)	792	1.04 (0.86–1.25)	618	1.03 (0.83–1.27)
≥13	375	0.86 (0.71–1.04)	283	0.82 (0.66–1.03)	334	0.87 (0.70–1.07)	249	0.85 (0.67–1.08)
Benign breast disease								
No	989	Ref	759	Ref	864	Ref	653	Ref
Yes	540	1.25 (1.10–1.41)	443	1.29 (1.12–1.49)	417	1.16 (1.01–1.33)	340	1.21 (1.04–1.40)
Surgery on the reproductive system								
No	1,293	Ref	1012	Ref	1,094	Ref	844	Ref
Yes	236	1.10 (0.96–1.28)	190	1.08 (0.91–1.28)	187	1.19 (1.01–1.40)	149	1.20 (1.00–1.44)

[†], model a includes age at menarche, age at first live birth, duration of breastfeeding, benign breast disease, surgery of the reproductive system, age at enrollment (continuous), education (low, medium, or high), BMI (underweight, normal, overweight or obese), smoking status (current, former or never-smoker), exposures to environmental tobacco smoke (yes or no), exposure to cooking smoke (none, little, some, or much), occupational exposures (yes or no), history of chronic respiratory disease (yes or no) and family history of lung cancer (yes or no). Province of different economic region was treated as a random variable considering within-cluster correlation. [‡], model b further includes menopause status and age at menopause based on Model a. HR, hazard ratio; CI, confidence interval.

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Table 4 Multivariable model for lung cancer risk among lifetime never–smokers

Factors	All females recruited				Postmenopausal females			
	Lung cancer		Adenocarcinoma		Lung cancer		Adenocarcinoma	
	Cases (N=1,454)	Model a[†], HR (95% CI)	Cases (N=1,143)	Model a[†], HR (95% CI)	Cases (N=1,220)	Model b[‡], HR (95% CI)	Cases (N=946)	Model b[‡], HR (95% CI)
Menopause status								
Natural menopause					1,140	Ref	875	Ref
Surgical menopause					80	1.67 (1.32–2.11)	71	1.83 (1.39–2.29)
Age at menopause, year								
<45					75	Ref	65	Ref
45–49					364	0.84 (0.65–1.09)	282	0.78 (0.59–1.03)
50–54					704	0.92 (0.72–1.18)	539	0.84 (0.65–1.10)
≥55					77	0.97 (0.70–1.35)	60	0.90 (0.63–1.29)
Age at menarche, year								
<13	129	Ref	103	Ref	95	Ref	75	Ref
13	250	1.11 (0.90–1.37)	191	1.16 (0.92–1.47)	208	1.21 (0.95–1.54)	158	1.17 (0.89–1.55)
14	345	1.15 (0.93–1.40)	259	1.17 (0.94–1.47)	284	1.21 (0.96–1.53)	206	1.13 (0.86–1.47)
15	292	1.24 (1.01–1.53)	240	1.42 (1.13–1.78)	242	1.27 (1.00–1.62)	198	1.34 (1.02–1.75)
≥16	438	1.46 (1.19–1.78)	350	1.58 (1.27–1.97)	391	1.52 (1.21–1.90)	309	1.54 (1.19–1.98)
Age at first live birth, year								
Nulliparous	26	1.07 (0.69–1.64)	20	1.09 (0.69–1.73)	20	1.16 (0.71–1.88)	16	1.24 (0.72–2.12)
<25	443	Ref	326	Ref	392	Ref	284	Ref
25–29	864	1.29 (1.14–1.45)	698	1.34 (1.18–1.53)	714	1.21 (1.06–1.38)	569	1.31 (1.13–1.52)
≥30	121	1.23 (0.99–1.51)	99	1.32 (1.05–1.66)	94	1.13 (0.90–1.43)	77	1.24 (0.95–1.61)
Duration of breastfeeding, month								
0	176	Ref	142	Ref	141	Ref	114	Ref
1–12	925	0.99 (0.83–1.18)	733	0.94 (0.78–1.14)	765	1.03 (0.85–1.25)	596	1.03 (0.83–1.28)
≥13	353	0.82 (0.67–1.00)	268	0.65 (0.53–0.81)	314	0.84 (0.68–1.05)	236	0.84 (0.66–1.08)
Benign breast disease								
No	960	Ref	738	Ref	838	Ref	635	Ref
Yes	494	1.24 (1.10–1.41)	405	1.30 (1.13–1.49)	382	1.15 (1.01–1.33)	311	1.21 (1.03–1.41)
Surgery on the reproductive system								
No	1,236	Ref	968	Ref	1,050	Ref	811	Ref
Yes	218	1.10 (0.94–1.27)	175	1.11 (0.95–1.31)	170	1.16 (0.98–1.37)	135	1.16 (0.96–1.41)

HR, hazard ratio; CI, confidence interval. †, Model a adjusted for age at menarche, age at first live birth, duration of breastfeeding, benign breast disease, surgery of the reproductive system, age at enrollment (continuous), education (low, medium, or high), BMI (underweight, normal, overweight or obese), smoking status (current, former or never-smoker), exposures to environmental tobacco smoke (yes or no), exposure to cooking smoke (none, little, some, or much), occupational exposures (yes or no), history of chronic respiratory disease (yes or no) and family history of lung cancer (yes or no). Province of different economic region was treated as a random variable considering within-cluster correlation. ‡, Model b adds menopause status and age at menopause to Model a.

For postmenopausal females, our findings are consistent with several previous studies that have noted elevated risks of lung cancer associated with surgical menopause (15,16,26). Many studies (17,18,20,25,33,36), although not all (19,21,22,24,31,37) have found positive associations with age at menopause. In our analysis, we initially observed no relationship of age at menopause to lung cancer risk. However, significant non-linear associations appeared in the cubic spline graph, which suggests that late (>50 years) menopause especially elevated the risk of lung cancer. Since the HRs below 45 also revealed increased lung cancer risk despite of the insignificant intervals, we considered that there may be a normal range (in a medical sense) for menopause age concerning the health status and lower lung cancer risk. Notably, some studies reported inverse associations between age at menopause and lung cancer risk (15,23,30,32,38), which are opposite to our findings. These opposite results were mainly attributed to different ethnicity. The recent meta-analysis (34) suggested that hormonal effects varied by population and race. For Western females, older age at menopause was significantly associated with decreased lung cancer risk, whereas more evidence was required for Asian females. We observed no association between lung cancer risk and the reproductive period, in agreement with most investigations (23,39), but in contrast with several studies that have noted either reduced (23) or increased (18) risks.

Consistent with an investigation that observed an inverse association concerning the time of breastfeeding to lung cancer risk (18), we noted a similar association for especially adenocarcinoma risk. Initially, we also observed an inverse association between the duration of breastfeeding and lung cancer risk. However, this association was not particularly convincing after adjustment for multiple covariates and other factors. Though breastfeeding was proved to be protective for females from breast and ovarian cancer (40), the role of breastfeeding in lung carcinogenesis still needs further clarity.

As sex-specific factors, estrogens are postulated as important agents in female cancer development and progression (14,41), which exhibits various physiological functions including regulation of the menstrual cycle and reproduction (42). Potential hormonal involvement in the etiology of lung cancer has been supported by a fair amount of experimental evidence, including abundant expression of estrogen receptors, progesterone receptors, and human epidermal growth factor receptors in both normal and tumor lung tissues (10-12). However, the potential biological mechanisms on this effect concerning lung cancer risk are still not clear. There is a speculation that the association between hormonal factors and lung cancer risk may be attributed to the cell proliferative properties of estrogen (43). However, this may be just an assumption and requires further evidence.

Our study had several strengths over previous studies. In contrast to the case-control designs, this prospective study allowed for extensive information collection at baseline with a large sample size. Confounding risk factors including smoking, exposures to environmental tobacco smoke and cooking fumes were all considered in our study. However, there were also some limitations. First, although we had relatively complete information on the most common risk factors, we were lacking data on exogenous hormonal factors, including the use of oral contraceptives, estrogen, and progestin, and hormone replacement therapy. Most previous studies (15,16,20,21,23,29,36,44,45) to date have claimed no significant association between exogenous hormonal factors and lung cancer risk. Therefore, this study only focused on endogenous hormonal factors. Detailed information on exogenous hormonal factors was also collected with a renewed questionnaire in 2019. In the next step, we plan to make further sufficient explorations of hormonal factors. Second, although our study may suggest that the role of hormonal factors in early life, those exposures that have close ties with hormonal factors, such as BMI and diet in adolescence, were unable to be measured in our study. Birth cohorts with long-term follow-up and monitoring are further required. Third, the data of exposure variables were collected based on a self-report questionnaire, which may be subject to misclassification and recall bias. Forth, the median follow-up time of this study was relatively short at 3.61 years. The number of identified new lung cancer cases was limited. Evaluations of weaker associations were precluded due to low case numbers, and analyses by subgroups were also restricted. In the context of this study, we will continue to follow up this cohort and make further sufficient explorations. Fifth, since the proportion of ever-smokers was extremely low in our study, we were unable to explain the association in current and former smokers. Therefore, we additionally performed sensitivity analysis in lifetime non-smoking females.

In conclusion, this study finds some support for the role of menstrual and reproductive factors in lung carcinogenesis. Later age at menarche, age at first live birth, age at menopause, and benign breast disease appeared to be predictive of elevated lung cancer risks. Duration

of breastfeeding was specifically associated with reduced adenocarcinoma risk. However, these relationships were somewhat complex, and required cautious interpretation. Therefore, further investigations addressing the biological mechanisms are needed. Additional studies on cellular changes in the lung tissue may help us further understand the role of hormonal risk factors in the etiology of lung cancer.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of China National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (number of IRB:15-070/997). Informed consent was taken from all individual participants.

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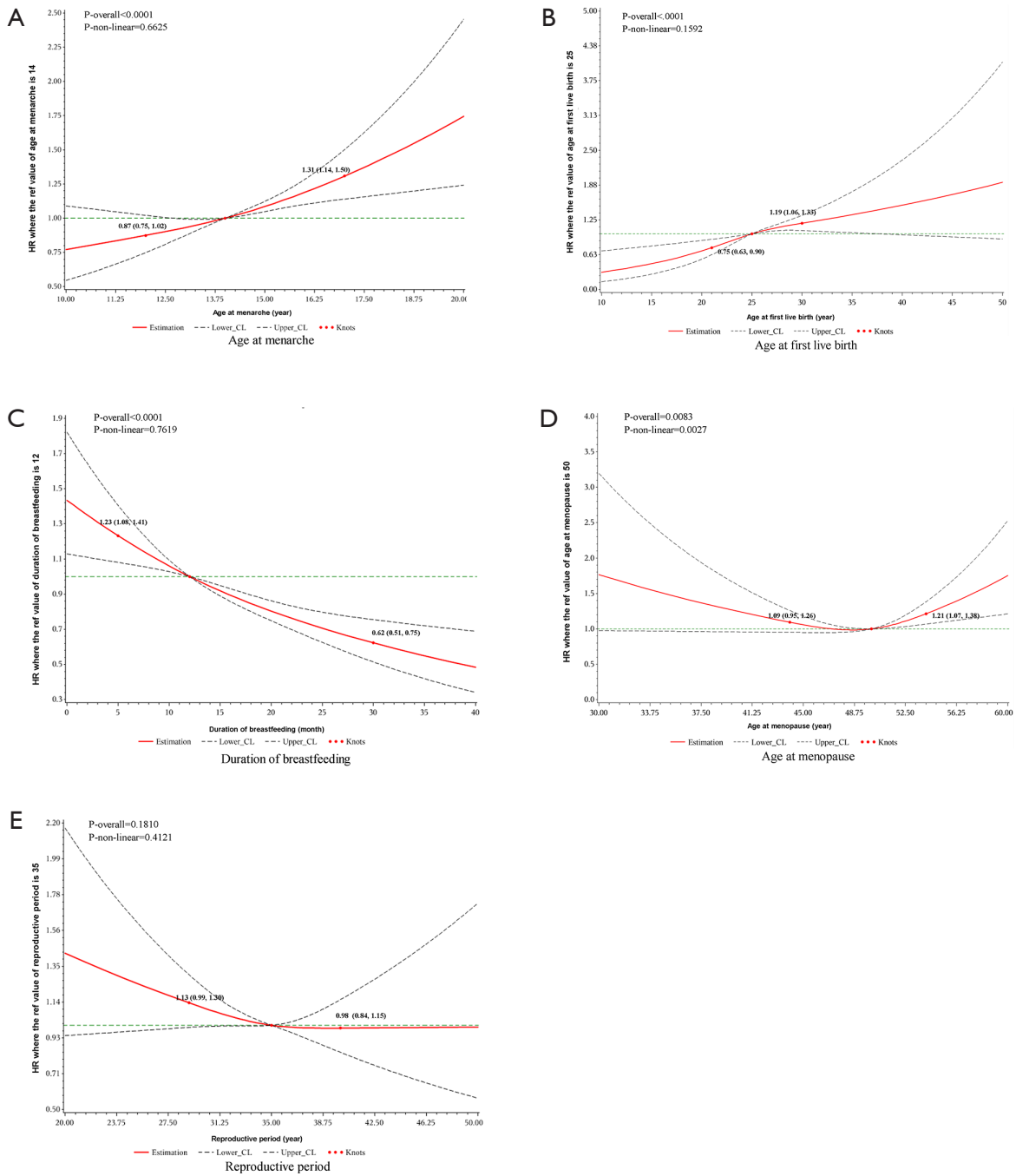
Figure S1 Cubic spline graph of the adjusted HR (represented by solid line) and 95% CI (represented by the dotted lines) for the association between menstrual and reproductive factors and adenocarcinoma risk. (A) Age at menarche, reference: 14 years old; (B) age at first live birth, reference: 25 years old; (C) duration of breastfeeding, reference: 12 months; (D) Age at menopause, reference: 50 years old; (E) reproductive period, reference: 35 years. Knots: 5th, 50th, 95th of the distribution. Analyses are adjusted for age at enrollment (continuous), education (low, medium, or high), BMI (underweight, normal, overweight or obese), smoking status (current, former or never-smoker), exposures to environmental tobacco smoke (yes or no), exposure to cooking smoke (none, little, some, or much), occupational exposures (yes or no), history of chronic respiratory disease (yes or no) and family history of lung cancer (yes or no).

Table S1 Characteristics and main findings of existed studies on the associations between menstrual, reproductive factors and lung cancer risk

Author	Study name	Country	Premenopausal Status	Number of participants	Never-smokers	Lung cancer cases	Years at enrollment	Median follow-up years	Main findings
Gallagher et al. 2013	Cohort Study of Shanghai female textile workers	Shanghai, China	Both pre and postmenopausal	267,400	N.A.	824	1989-1991	9.3	Increased lung cancer risk: surgical menopause. Decreased lung cancer risk: parity.
Weiss et al. 2008	Shanghai Women's Health Study	Shanghai, China	Both pre and postmenopausal	71,314	71,314	220	1996-2000	4.1	Decreased lung cancer risk: later age at menopause, longer reproductive period, higher parity, intrauterine device use.
Tan et al. 2015	The Singapore Breast Cancer Screening Project	Singapore	Postmenopausal	28,222	26,473	311	1994.10-1997.02	15.8	Decreased lung cancer risk: higher parity.
Seow et al. 2009	The Singapore Chinese Health Study	Singapore	Postmenopausal	35,298	N.A.	298	1993.04-1998.12	9.6	Decreased lung cancer risk: higher parity.
Jeon et al. 2020	The Korean National Health Insurance System based	Korea	Postmenopausal	4,775,398	4,335,259	16,556	2009-2014	4.4	Nonsignificant associations.
Wilunda et al. 2021	The Japan Public Health Center-based Prospective Study	Japan	Both pre and postmenopausal	42,615	42,615	400	1990–1994	21	Increased lung cancer risk (adenocarcinoma specific): longer fertility span, late age at menopause, natural menopause, or surgical menopause. Decreased lung cancer risk: breastfeeding.
Lui et al. 2005	The Japan Public Health Center-based Prospective Study	Japan	Both pre and postmenopausal	44,677	44,677	153	1990–1994	8–12	Increased lung cancer risk: early age at menarche and late age at menopause.
Schwartz et al. 2015	The Women's Health Initiative studies	U.S.	Postmenopausal	160,855	81,031	2,467	1993.10-1998.12	14	Decreased lung cancer risk: later age at menopause, higher parity.
Brinton et al. 2011	The NIH-AARP Diet and Health Study	U.S.	Postmenopausal	185,017	84,262	3,512	1995-1996	5.7	Increased risk: early age at ovarian cessation. Decreased lung cancer risk: later age at menarche.
Baik et al. 2010	The Nurses' Health Study	U.S.	Postmenopausal	107,171	48,227	1,729	1984	22	Increased lung cancer risk: earlier age at menopause, exogenous hormone use, age at first birth (among never smokers). Decreased lung cancer risk: parity (among never smokers).
Kabat et al. 2007	Canadian National Breast Screening Study	Canada	Postmenopausal	89,812	45,065	750	1980-1985	16.4	Increased lung cancer risk: higher parity. Decreased lung cancer risk: later age at first live birth.